Regional Oral History Office
The Bancroft Library

University of California
Berkeley, California

Program in the History of the Biological Sciences and Biotechnology

Dennis G. Kleid, Ph.D.

SCIENTIST AND PATENT AGENT AT GENENTECH

With an Introduction by
Coe A. Bloomberg

Interviews Conducted by
Sally Smith Hughes, Ph.D.
in 2001 and 2002

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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Dennis G. Kleid, 2002

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BIOTECHNOLOGY SERIES HISTORY--Sally Smith Hughes, Ph.D.

Genesis of the Program in the History of the Biological Sciences and Biotechnology

In 1996 The Bancroft Library launched the Program in the History of the Biological Sciences and Biotechnology. Bancroft has strong holdings in the history of the physical sciences--the papers of E.O. Lawrence, Luis Alvarez, Edwin McMillan, and other campus figures in physics and chemistry, as well as a number of related oral histories. Yet, although the university is located next to the greatest concentration of biotechnology companies in the world, Bancroft had no coordinated program to document the industry or its origins in academic biology.

When Charles Faulhaber arrived in 1995 as Bancroft's director, he agreed on the need to establish a Bancroft program to capture and preserve the collective memory and papers of university and corporate scientists and the pioneers who created the biotechnology industry. Documenting and preserving the history of a science and industry which influences virtually every field of the life sciences and generates constant public interest and controversy is vital for a proper understanding of science and business in the late twentieth and early twenty-first centuries.

The Bancroft Library is the ideal location to carry out this historical endeavor. It offers the combination of experienced oral history and archival personnel and technical resources to execute a coordinated oral history and archival program. It has an established oral history series in the biological sciences, an archival division called the History of Science and Technology Program, and the expertise to develop comprehensive records management plans to safeguard the archives of individuals and businesses making significant contributions to molecular biology and biotechnology. It also has longstanding cooperative arrangements with UC San Francisco and Stanford University, the other research universities in the San Francisco Bay Area.

In April 1996, Daniel E. Koshland, Jr. provided seed money for a center at The Bancroft Library for historical research on the biological sciences and biotechnology. And then, in early 2001, the Program in the History of the Biological Sciences and Biotechnology was given great impetus by Genentech's generous pledge to support documentation of the biotechnology industry.

Thanks to these generous gifts, Bancroft has been building an integrated collection of research materials--oral history transcripts, personal papers, and archival collections--related to the history of the biological sciences and biotechnology in university and industry settings. A board composed of distinguished figures in academia and industry advises on the direction of the oral history and archival components. The Program's initial concentration is on the San Francisco Bay Area and northern California. But its ultimate aim is to document the growth of molecular biology as an independent field of the life sciences, and the subsequent revolution which established biotechnology as a key contribution of American science and industry.

Oral History Process

The oral history methodology used in this program is that of the Regional Oral History Office, founded in 1954 and producer of over 2,000 oral histories. The method consists of research in primary and secondary sources; systematic recorded interviews; transcription, light editing by the interviewer, and review and approval by the interviewee; library deposition of bound volumes of transcripts with table of contents, introduction, interview history, and index; cataloging in UC Berkeley and national online library networks; and publicity through ROHO news releases and announcements in scientific, medical, and historical journals and newsletters and via the ROHO and UCSF Library Web pages.

Oral history as a historical technique has been faulted for its reliance on the vagaries of memory, its distance from the events discussed, and its subjectivity. All three criticisms are valid; hence the necessity for using oral history documents in conjunction with other sources in order to reach a reasonable historical interpretation.[1] Yet these acknowledged weaknesses of oral history, particularly its subjectivity, are also its strength. Often individual perspectives provide information unobtainable through more traditional sources. Oral history in skillful hands provides the context in which events occur--the social, political, economic, and institutional forces which shape the course of events. It also places a personal face on history which not only enlivens past events but also helps to explain how individuals affect historical developments.

Emerging Themes

Although the oral history program is still in its initial phase, several themes are emerging. One is "technology transfer," the complicated process by which scientific discovery moves from the university laboratory to industry where it contributes to the manufacture of commercial products. The oral histories show that this trajectory is seldom a linear process, but rather is influenced by institutional and personal relationships, financial and political climate, and so on.

Another theme is the importance of personality in the conduct of science and business. These oral histories testify to the fact that who you are, what you have and have not achieved, whom you know, and how you relate have repercussions for the success or failure of an enterprise, whether scientific or commercial. Oral history is probably better than any other methodology for documenting these personal dimensions of history. Its vivid descriptions of personalities and events not only make history vital and engaging, but also contribute to an understanding of why circumstances occurred in the manner they did.

Molecular biology and biotechnology are fields with high scientific and commercial stakes. As one might expect, the oral histories reveal the complex interweaving of scientific, business, social, and personal factors shaping these fields. The expectation is that the oral histories will serve as fertile ground for research by present and future scholars interested in any number of different aspects of this rich and fascinating history.

Location of the Oral Histories

Copies of the oral histories are available at the Bancroft, UCSF, and UCLA libraries. They also may be purchased at cost through the Regional Oral History Office. Some of the oral histories, with more to come, are available on The Bancroft Library's History of the Biological Sciences and Biotechnology Website: http://bancroft.berkeley.edu/Biotech/.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
October 2002

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[1]The three criticisms leveled at oral history also apply in many cases to other types of documentary sources.

December 2002

ORAL HISTORIES ON BIOTECHNOLOGY

Program in the History of the Biological Sciences and Biotechnology

Paul Berg, Ph.D., "A Stanford Professor's Career in Biochemistry, Science Politics, and the Biotechnology Industry," 2000

Mary Betlach, Ph.D., "Early Cloning and Recombinant DNA Technology at Herbert W. Boyer's UCSF Laboratory," 2002

Herbert W. Boyer, Ph.D., "Recombinant DNA Science at UCSF and Its Commercialization at Genentech," 2001

Thomas J. Kiley, "Genentech Legal Counsel and Vice President, 1976-1988, and Entrepreneur," 2002

Dennis G. Kleid, Ph.D., "Scientist and Patent Agent at Genentech," 2002

Arthur Kornberg, M.D., "Biochemistry at Stanford, Biotechnology at DNAX," 1998

Fred A. Middleton, "First Chief Financial Officer at Genentech, 1978-1984," 2002

Thomas J. Perkins, "Kleiner Perkins, Venture Capital, and the Chairmanship of Genentech, 1976-1995," 2002

"Regional Characteristics of Biotechnology in the United States: Perspectives of Three Industry Insiders" (Hugh D'Andrade, David Holveck, and Edward Penhoet), 2001

Niels Reimers, "Stanford's Office of Technology Licensing and the Cohen/Boyer Cloning Patents," 1998

William J. Rutter, Ph.D., "The Department of Biochemistry and the Molecular Approach to Biomedicine at the University of California, San Francisco: Volume I," 1998

Robert A. Swanson, "Co-founder, CEO, and Chairman of Genentech, 1976-1996," 2001

Daniel G. Yansura, "Senior Scientist at Genentech," 2002

Oral histories in process:
Brook Byers
Stanley N. Cohen
Chiron Corporation
Roberto Crea
David V. Goeddel
Herbert Heyneker
Irving Johnson
Arthur Levinson
G. Kirk Raab
William J. Rutter, Volume II
Richard Scheller
Axel Ullrich
Keith R. Yamamoto

INTRODUCTION by Coe A. Bloomberg

Dennis Kleid has proven to be a unique resource at Genentech. He combines a knowledge of Genentech's scientific contributions, from the very beginnings of Genentech, with an understanding of the litigation process. Dennis received a Ph.D. in organic chemistry from the University of Pittsburgh in 1972. Following post-doctorate fellowships at MIT and Harvard, he worked as a bio-organic chemist at Stanford Research Institute from 1975-1978. Later in 1978, he became Employee Number Five at Genentech as a molecular biologist. Because employees one to four are no longer at Genentech, Dennis's tenure is longer than that of any other Genentech employee. Dennis worked as a scientist at Genentech until 1986 when he joined Genentech's Legal Department. He is admitted to practice before the U.S. Patent and Trademark Office as a Patent Agent, and his current title at Genentech, Senior Patent Agent and Senior Scientist, reflects the fact that he has one foot in the field of law, and the other in the field of science.

Because of Dennis's familiarity with the various scientific projects at Genentech, he is ideally suited to assist litigation counsel in determining what documentation should be reviewed, and what Genentech scientists should be interviewed, in connection with patent litigation. He is a very patient teacher of lawyers with respect to complicated scientific issues such as the recombinant DNA production of pharmaceutical products. He has been involved in virtually every major patent dispute in which Genentech has been involved in the last 15 years. And over that time, he has developed a keen grasp of the legal issues that are often determinative of patent litigation and patent interferences. On a more personal note, Dennis has a wonderful, if somewhat irreverent, sense of humor, and is an absolute pleasure to work with.

Coe A. Bloomberg
Partner--Jones, Day, Reavis & Pogue

November 20, 2002

INTERVIEW HISTORY--Dennis G. Kleid

Dennis Kleid as one of the first three scientists hired on site at Genentech is an obvious choice for interviews on the company's history. Unlike most others in this series, he has remained at Genentech and hence was an apt observer of corporate science and culture as the company grew and prospered over time. In 1986 Kleid made a substantial career shift to Genentech's legal department where he continues to serve as patent agent. He can thus speak from personal experience of both the scientific and legal aspects of Genentech.

The detailed narrative which Kleid recounts in the following pages is directly informed by his two complementary positions. One "voice" is that of the scientist deeply knowledgeable in chemistry and molecular biology. A second "voice" is that of the legal expert whose scientific background and participation in specific research projects is instrumental in preparing and sustaining Genentech's legal team in the seemingly endless litigation typical of the biotechnology industry. The reader will find that Kleid's direct experience of much of the early research that transpired at Genentech is refreshed, extended, and inevitably molded by his ongoing review of the scientific and intellectual property background to patent interferences and other litigation. "My job," he remarked off tape, "is doing history in reverse."

The Oral History Process

Six interviews were recorded in Kleid's office in Building 25 at Genentech. He was a ready and enthusiastic subject. He provided a detailed outline of interview topics which guided the recorded sessions as well as documents to supplement the discussion. Kleid's preoccupation with the factual basis of Genentech's achievements and setbacks carried over into the transcript review process. He added new textual material in a few cases and a flotilla of footnotes, evidence of the scientist-cum-legal expert's attention to full documentation. We are grateful for the considerable work this represents. His expressed wish is to provide the reader with references to back up his narrative. As always with the oral histories supported by Genentech, the transcripts were submitted for review by its legal department. No changes were requested.

One might expect the man behind this labor-intensive effort to be sober and humorless. One could not be further from the mark. Although intently serious about his scientific and legal responsibilities, Dennis Kleid laughs easily, exudes a "laid-back" California style, and appears quite happy to share his views. Getting him to talk in the interviews was not a glimmer of a problem.

Sally Smith Hughes, Ph.D.
Historian of Science

Regional Oral History Office
The Bancroft Library
University of California, Berkeley
November 2002

Regional Oral History Office
Room 486 The Bancroft Library

University of California
Berkeley, California 94720

BIOGRAPHICAL INFORMATION

(Please write clearly. Use black ink.)

Your full name Dennis G. Kleid

Date of birth July 25, 1946 Birthplace Napa, California

Father's full name Albert H. Kleid

Occupation Machinist, Assembly Sp. Birthplace New York, N.Y.

Mother's full name Alna M. Kleid

Occupation Accountant Birthplace Santa Rosa, Calif.

Your spouse/partner Michelle M. Kleid

Occupation Reg. Nurse, Clinical Res. Birthplace Seattle, Washington

Your children Jonathan J. Kleid, Suzanne D. Kleid
Adrienne D. Kleid

Where did you grow up? Napa, California

Present community Foster City, California

Education B.S. degree Chemistry, Univ. of Calif. Berkeley, Calif.
Ph.D. degree Organic Chemistry, Univ. of Pittsburgh, Penna.

Occupation(s) Sr. Scientist, Sr. Patent Agent

Areas of expertise Molecular Biology, Immunology, Patent Law

Other interests or activities Second Home, Maui, Hawaii, Golf

Organizations in which you are active Amer. Assoc. Adv. Science
Amer. Chem. Soc.

SIGNATURE Dennis G. Kleid DATE: Nov 8, 2002

INTERVIEW WITH DENNIS G. KLEID

I FAMILY BACKGROUND AND EDUCATION

[Interview 1: November 16, 2001] ##[1]
[South San Francisco, CA]

Family History and Undergraduate Education

Hughes: Please give me a thumbnail sketch of your family of origin, going back a reasonable distance.

Kleid: On my mother's side going back a reasonable distance would be before the Revolutionary War. The Huguenots emigrated to the States in the 1600s and her family dates all the way back to that time.[2] Her family's ancestors came to California after the Civil War from Georgetown, South Carolina.[3] Her great-great-grandfather's family had ten kids and all five of the sons who fought as part of the Confederate South survived the Civil War. At the end, when they all came back home, they decided that they would emigrate to California. Two of the sons[4] went across the Isthmus of Panama and took a boat up to San Francisco,[5] taking with them a letter of introduction to a Dr. H. H. Toland, a former resident of Columbia, South Carolina, then a

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[1]## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

[2]Leonard Dozier came from France in 1686, Jeromie Cothonneau came from France in 1688. (Unless attributed to SSH, the interviewer, all footnotes are by Dr. Kleid.)

[3]Anthony White Dozier 1801-1870 and Mary Catherine Cuttino Dozier 1811-1873 and family including William Gaillard Dozier 1833-1908, Peter Cuttino Dozier 1835-1877, Leonard Franklin Dozier 1835-1917, Virginia Ellen Dozier 1838-1925, Anthony White Dozier 1842-1874, Edward Charles Dozier* 1843-1919, Melvile Dozier 1846-1936, Alvin Dozier 1848-1921, Barton Dozier 1851-1931 and Linwood Dozier 1855-1886. (*My mother's great-grandfather)

[4]Leonard and Melvile.

[5]The Oregonian entered the Golden Gate March 12, 1868.

leading physician in San Francisco. He founded Toland Hospital and the School of Medicine.[1] Toland Hall is right there on Parnassus Avenue, and as a coincidence, it's right next to the building that Herb Boyer's lab was in when I first met Herb Boyer in the mid-seventies.[2] I also went to University of Pittsburgh and that's where Herb Boyer went. I also met some of his postdocs at different meetings. So I had quite a number of coincidental path-crossings with Herb Boyer in the mid-seventies.

On my father's side they're Jews that emigrated at the turn of the century to New York City.[3] My father (Albert H. Kleid), came out to California during World War II . My mother picked him up when he was hitchhiking. That's how she (Alna M. Kleid), met my father. They got married just after World War II ended, and soon after that, that's when I was born, July 1946. I'm part of the oldest Baby Boomers, I guess.

Hughes: Where were you brought up?

Kleid: I was born and raised in Napa, California. When I graduated from high school, I went to Napa Junior College for a couple of years, and then I went to the University of California at Berkeley [1965-1968]. I somehow graduated from Berkeley in organic chemistry. It was very difficult for me, and I just barely made it through Berkeley. One of my classes was in molecular biology and my professor was Gunther Stent. He gave a wonderful course and I fell in love with molecular biology at that time.[4]

When I graduated from Berkeley I really just wanted to get a job, but in the early seventies there weren't a lot of jobs for kids out of college. It was an economic time rather like today's recession. Just in case, I sent away for applications for graduate school. I got six applications, and I ended up filling out the three easiest ones. The University of Pittsburgh accepted me with a teaching assistantship. So this guy from California ended up in Pittsburgh, Pennsylvania at the University of Pittsburgh--like I said, the same place where Herb Boyer also was a student at one time.

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[1]He bequeathed these institutions to the University of California which are now known as U.C. Medical Center.

[2]Dr. Boyer founded Genentech in 1976.

[3]Jacob Kleid (my dad's father), entered the U.S. via Ellis Island with his sister and parents prior to 1900. The family immigrated from the Galicia region, at that time part of the Austrian Empire.

[4]Gunther S. Stent, *Molecular Biology of Bacterial Viruses*, San Francisco, London, W. H. Freeman and Company, 1963. [SSH]

Family of Origin

Hughes: Let's pick up some of these strands. What did your mother and father do for a living and how many brothers and sisters did you have?

Kleid: I had two brothers and a sister. My father worked at the University of California Lawrence Radiation Lab as a machinist's specialist. He helped build the atom smashers. He did metal working.

Hughes: Did he know the Lawrences?

Kleid: He didn't know the Lawrences, but he worked with Donald Glaser a lot.

Hughes: Of the bubble chamber.

Kleid: The bubble chamber, yes! My father worked on the bubble chamber. I think the last project he did before he retired was the target for the Stanford linear accelerator. So he would come home with stories of the projects he was working on and he is still today very proud of being part of the Lawrence laboratories back then.

Hughes: Did his profession have anything to do with your choice of science?

Kleid: He certainly instilled an interest in science, although he didn't finish high school until he came to California and did high school at night school. And then he took college courses at night school. He talked a lot about what they were learning about breaking the atoms apart and making new atoms. I was definitely very interested in that. From a very young age, third or fourth grade, I was going to be a scientist. It was really the only thing that I ever really wanted to do.

Hughes: Was education a priority in the family?

Kleid: It was, yes. My folks really wanted us to do well in school, and they were very happy that we were going to college.

Hughes: Where do you fall in the family ranking?

Kleid: I was the oldest son and then I had two younger brothers, but we were all very, very close in age. My one brother Don was just a year younger and my brother Ken was three years younger, but our birthdays were all within a couple weeks of each other; we're all Leos. So we used to fight all the time and pummel each other.

Hughes: Did any of them end up in science?

Kleid: No. My brother Don went to UC Davis and became a math teacher. He still teaches math at Folsom High School. My brother Ken didn't go to college. He went to Mare Island, to a school that provided technical training. I think he studied sonars. He said, "I did that for mom." After two years, he started driving around the United States and ended up in Hawaii. He was

friends with some people from Napa who invented the windsurfer, and he used to give windsurfer lessons in Kailua, which is on the windward side of Oahu opposite Honolulu. Then he did more of that windsurfer renting and teaching on Kauai and Maui.

Hughes: Say a word or two about your mother.

Kleid: My mother also went to school when I was younger and took classes and finished high school. She became a bookkeeper for Kaiser Steel. She worked at the Kaiser plant in Napa from when I was in high school until she retired, about ten, fifteen years ago. My father also worked at Kaiser in the 1950's before he got the job at Berkeley. Napa to Berkeley, that was a very long commute. That was very hard on him.

Undergraduate Education, 1964-1968

Choosing a Major and Napa Junior College

Hughes: You said that organic chemistry was a struggle, or words to that effect.

Kleid: College was a struggle. [laughter]

Hughes: Why did you choose organic chemistry?

Kleid: I actually chose it in high school. I took biology and that was interesting, and then I took chemistry, and I liked that way better. Then I took physics and I said, "No, I like chemistry better."

Hughes: Why?

Kleid: Something about the molecules and how they interact with each other was interesting to me, and you could understand it without a lot of math. Biology was too heavily based on phenomenology, and I couldn't really understand what was going on. But with atoms, you could really imagine how they hooked together. It just seemed interesting to me. So I kept with chemistry.

I went to Napa Junior College because I had a very hard time with writing and reading. I'm slightly dyslexic, and I have a hard time writing. One of the requirements for chemistry was that you had to learn German. I was extremely poor in that, so I decided with some encouragement from my mom to go to Napa J.C. and take basic courses, and then when I went to Berkeley I could focus on the science part. That worked out pretty well.

UC Berkeley, 1965-1968

Kleid: I got through Napa J.C. okay, but then when I switched to Berkeley the classes were just incredibly difficult. In my first term I got two C's and a C minus, so I was on probation. Next time I got all C's. If you got below a C average for three quarters in a row they kicked you out. So the third quarter I got two C's and a B, which canceled out the C minus. But one of the C's was in physics, and it turned out that I flunked the physics final--I got absolutely zero on it. The teaching assistant was very, very nice. He convinced the professor to give me a C in the class because of what I did on a day-to-day basis in class, or else I would have been gone from Berkeley. The senior year was better. I was there for seven straight quarters and somehow made it out of Berkeley.

Hughes: Did you have any particular contact with the faculty?

Kleid: Not really. Berkeley's impersonal for undergrads. My professors were down on a stage in the bottom of a giant auditorium. I didn't get to know any professors at all.

Graduate Student, University of Pittsburgh, 1968-1972

Marriage

Hughes: Then the University of Pittsburgh. What laboratory did you end up in?

Kleid: When I went there I didn't know whose lab I was going to be in. I had a very hard time adjusting to the University of Pittsburgh because it was just so different than California.

Hughes: You had never been out of California?

Kleid: My folks had driven to Washington DC and NYC in 1964 with my grandparents in two cars and a trailer, but that was it. Prior to that, I crossed the border to Oregon once and went to the Nevada side of Lake Tahoe of few times. But Pittsburgh was really different. In the early seventies it had all these steel companies within the city limits. So it was a smoky place and smelled sulfury and buildings were all drippy looking. I had a very hard time finding a place to live, but finally I found a place and started adjusting to life there.

I had a girlfriend from Berkeley, and I had proposed to her. But we didn't end up getting married so we corresponded with each other. Then she decided that she was going to come to Pittsburgh, and we were going to get married in Pittsburgh. She told her folks that and they said, "No, no, let's bring him back." So within three or four months of arriving in Pittsburgh I came back to California, got married, and took her [Phyllis L. Innerfield Kleid] back to Pittsburgh. We lived in an old house on Nicholson Street--which is this old cobblestone street--on the third floor in this house chopped up into three rental units. We stayed there for four years--slanty ceilings and everything.

In Pittsburgh I had again the issue of not being able to read and write very well, and here I was in graduate school. I didn't do very well on a couple of tests, so I was on probation there as well but somehow made it through. Luckily, today we have computers and word processors. It's just totally different.

Toby Chapman's Laboratory

Kleid: I picked a professor, Toby Chapman, who was brand new at Pitt. I think he got there the year before I arrived. He was interested in making peptides, but he also had a project on making DNA, actually synthesizing DNA was what he wanted me to do. When I interviewed professors to see which one I wanted to work with, I really got attracted to the DNA part because of that course I took from Gunther Stent. DNA seemed really interesting to me. Dr. Chapman was the only guy in the organic chemistry department who was working on DNA.

Hughes: You were at Pittsburgh from '68 through '72?

Kleid: That's right. So it would probably be 1969 when we chose which professor we were going to work with. In '69 I decided that DNA was what I wanted to work on.

Stent had told us in his course on molecular biology all about the genetic code, how that was sorted out, and how phages work. He said: "That's all understood now. It's really too bad you guys missed the really exciting part of molecular biology."

Hughes: He wrote a book to that effect.[1]

Kleid: So here I am at Pittsburgh and I decide that DNA was the thing I'd like to study.

Hughes: That was a little unusual for an organic chemist, wasn't it?

Kleid: There were almost no organic chemists in the area of DNA, especially making DNA. Everybody in the literature was related to one particular guy, Dr. Gobind Khorana. Khorana's students had quite a few papers and had made quite a bit of progress. During the time I was in graduate school he got the Nobel Prize for solving the genetic code, which he shared with Marshall W. Nirenberg and Robert W. Holley.

Nirenberg did an experiment where he had an RNA polymer of U's [uracils] and showed that when he translated that in vitro he got phenylalanine. That was the conceptual breakthrough that allowed you to sort out the genetic code. So U-U-U coded for phenylalanine. What Khorana did was kind of take a sledgehammer to the project. He made every single possible combination of three letters in RNA and solved the genetic code and all the codons.

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[1]Gunther S. Stent, *The Coming of the Golden Age: A View of the End of Progress*, Garden City, NY: Natural History Press, 1969. [SSH]

DNA Synthesis

Kleid: Toby Chapman, who came from Elkin Blaut's lab, was interested in making new chemistry to synthesize peptides, and he thought that some of his ideas for making peptides might be applied to DNA molecules. He wanted me to try to link one nucleotide to another nucleotide, using a different kind of phosphate chemistry than was available at the time. So that's what I worked on for the four years. I was trying to do the chemistry of making DNA molecules.

Hughes: And how did his method--or probably by then your method--work?

Kleid: Actually, it was way before its time. The idea was to activate a phosphate so that when you added a hydroxyl group from the next nucleotide, it would join up and eliminate this active phosphate. Toby had worked on that with amide bonds where they had made active esters for making peptides, so he thought maybe we could [do] that with active phosphates. So I tried. I think the machines today that make DNA use that kind of concept. But back then it was just impossible--for me anyway.

Some of the problems were that you needed to keep everything absolutely dry. Every single molecule of water that was in your reaction tube messed it up so you really couldn't do it. We tried all kinds of dry boxes. And here we were in this old chemistry lab in Pittsburgh which was built at the turn of the other century, and it had no air conditioning and the windows were open. It was just humid as heck there all summer and cold and dry all winter long, so I couldn't get any of these reactions to work consistently.

Hughes: How much was Chapman involved?

Kleid: This was his first try at this kind of work, so he was just drawing on the blackboard different things to try.

Hughes: And you were having to go back to the lab bench and do it.

Kleid: Right. And at the same time take courses. And I was very involved with teaching because I was a teaching assistant--that's how I survived, with the paycheck. So there wasn't a lot of time. Graduate students don't actually have a lot of time to do research. I was very committed to getting out of Pittsburgh in four years. There are a lot of graduate students who last a long time but I wanted <u>out</u> of there very badly.

Hughes: Because you didn't like the area?

Kleid: The sun never shines in Pittsburgh; the winter starts on a particular day almost every year. Early November the snowflakes would start falling. It was just very difficult there. My bride and I, after a year there, saved up enough money to buy a Pontiac for $300. And of course it was stolen the first day. Luckily we got it back that same day. The rent was $100 a month and I was making $200 a month. It was tough.

Hughes: Was your wife in school?

Kleid: Not initially. She worked in the sociology department at Pitt, so she was making a little bit to help out and taking some courses. She eventually got a master's degree in special education. We had a hard time in Pittsburgh, so we both wanted to go home.

Academic Challenges

Kleid: In about the third year of graduate school I was making it through all the courses except my grades were still just a little bit too low. The professors decided whether I would be in the Ph.D. program or whether I would end with a master's degree.

Hughes: Were they making any compensation for the fact that you were dyslexic?

Kleid: No, I never talked about it, and they never realized it. Nobody ever paid any attention to anything like that. In those days the judgement was you just weren't working hard enough.

Hughes: Which was not the case, was it?

Kleid: I was working my buns off!

The whole chemistry faculty met to discuss my situation. I was taking one course and my professor Toby Chapman and the course professor Foil Miller both knew that I wasn't going to get the needed B+ in that course. The vote was ten to ten to take up my case that day or wait until I finished this one course. The chairman of the department Dr. Wallace broke the tie and said, "Let's take up his case now." My professor said a whole bunch of nice things about what I was doing in the lab. Another professor, Dr. Sam Danishevsky, talked about how I was doing his organic chemistry course and a special night course he gave. The professor I worked for as a TA, Dr. Alfred Moye, said I was doing a really great job. Then this old professor, Dr. Henry Frank who discovered water structure at the turn of the last century I think, explained, "Sometimes scientists don't do that well in courses. I don't think that has much to do with being a good scientist." So they unanimously let me in the Ph.D. program. I got a C- in that course so I would have been out.

Pursuing DNA Synthesis

First Visit to Gobind Khorana's Laboratory, MIT

Kleid: A while after that my professor and I talked about what I was going to do next, after my Ph. D. thesis. I said that I would really like to do a postdoc in Dr. Khorana's lab. By that time his research team had followed up the work on the genetic code with synthetically making whole genes. They had made a gene that encoded a transfer RNA. It was about sixty or eighty nucleotide units long. It was a major project. Those people really knew what they were doing,

so I asked Dr. Chapman if he could help me get a postdoc position there. Dr. Chapman helped arrange that, and I gave an interview at MIT, which is where Khorana was by that time. Originally he was in British Columbia and then he was in Madison, Wisconsin. After my talk about my trials and tribulations with active esters, Khorana said that he would consider me in his lab if I got a postdoctoral fellowship grant. He said he would be happy to sign his name on a proposal, so that's what I did.

In the three or four days I was at MIT on this trip and interview, I saw how they were making DNA. Even though there were a lot of publications on the chemistry, you don't see the equipment, how they were doing it, how they were watching out for the water--making sure everything was absolutely dry. They had all these different instruments and equipment to keep every single molecule of water away.

Hughes: Information you couldn't get by reading the articles?

Kleid: No, not the equipment part; I was using all the wrong things.

Graduate Thesis Project on DNA Synthesis

Kleid: I came back from that trip and said to Dr. Chapman, "Here's a project that I would really like to do: I'd like to make the DNA while its hooked onto a polymer and join nucleotides to nucleotides and use chemistry that was more like they were using at MIT. One of the ideas we talked about was getting away from active esters and doing the joining a more traditional way. I worked on that for the last six or eight months while in Pittsburgh.

The project in my Ph. D. thesis was on making T-T-T, three T's [thymidines] in a row. I think I spent about four or five months hooking T and T and T together.[1] It doesn't seem like it would take that long, right? But it did. I wrote up and then defended my thesis on this plus a review on the methods used to make DNA that were in the literature at that time.[2]

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Kleid: I still remember the questions I was asked. One question was from Sam Danishevsky, who is now a very famous organic chemist. I think he went to Yale and then Sloan Kettering in New York City. His question was, "How do you know the difference between messenger RNA,

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[1]T.M. Chapman and D.G. Kleid, Oligonucleotide synthesis on polar polymer supports. The use of a polypeptide support, J.C.S. Chem. Commun. 1973, 193-194. Reprinted in *Benchmark Papers in Organic Chemistry*, Vol. 2, E.C. Blossey and D.C. Neckers (eds.), Dowden, Hutchinson and Ross Inc., Stoudsburg, Penn., 1975, p. 214.

[2]D.G. Kleid, Synthesis of oligonucleotides. Dissertation Abstracts International B 33(8), 3555-B (1973).

transfer RNA, and ribosomal RNA?" This is pretty basic stuff. [laughter] So I did fine on the thesis, and then I went to MIT.

Postdoctoral Student, Khorana's Lab, MIT, 1972-1974

Colleagues and the Diester Method

Kleid: When I got to MIT I soon realized that I would be one of the token Americans in Khorana's group. It turns out that most everybody there were postdoctoral fellows from Europe and all around the world. He got his major support from government grants for the facility, materials, and things like that, but all these people brought their own fellowship money. It was just an incredible group of people. I was just so impressed and felt so lucky to be part of that group. One of the people that I got to know was named Kan Agarwal, (he was from India), and an absolute genius. He was a child genius.

Hughes: I noticed Agarwal's name on some of your papers.

Kleid: Right. He worked right next to me, and we became incredibly good friends. His family were not the traditional Hindu, because they ate meat. His parents were live-in helpers for a British family, and he and his brother were encouraged by this British family to go to an English boarding school. He got shipped away to school when he was just a little kid, and he never really went home again. Eventually, he made it to London and studied with some of the most famous scientists there are, and then got this position with Khorana in the U.S. He had been with Khorana for about ten years when I met him. So here was this kid about my age who in his whole life only knew science and school. But he was so interesting. I just totally enjoyed that guy.

Hughes: Did you end up collaborating?

Kleid: We did. He taught me how to make DNA. On his bench, I made my first DNA, which was twelve nucleotide units long. It took six months to make one oligonucleotide twelve units long. The sequence that I was making resulted from one of the very first DNA sequencing experiments ever done. In that lab they not only did chemistry of making DNA, they also developed the early methods of DNA sequencing. This was a little piece of DNA with a sequence from just past the coding sequence of a transfer RNA. Khorana and his group had decided, "With the transfer RNA's coding sequence, we're also going to make the DNA on either side of it." The goal of Khorana's group was to make a completely synthetic gene in the lab and in the test tube show that it functions.

Hughes: Were all these different people aiming at that very goal?

Kleid: Everybody in the lab, and there were about twenty. This project had taken already a couple years when I joined. So there were twenty or thirty postdoc years on this one project to chemically make a gene in a test tube and show that it works.

Hughes: Was your experience using the solid-phase technique of interest to them?

Kleid: No. They had the methods they were happy with.

Hughes: The diester?

Kleid: Exactly. It was very slow and painstaking, but the DNA product at the end of the day was extremely pure. You could assemble all these pieces together to make this gene--but you had to have very, very pure DNA to do that.

Hughes: Nobody else at that time was making such pure DNA?

Kleid: No. Some of Khorana's former students were working on this at other universities, and they were trying new methods. Some were at that time competitors who thought they could make DNA a different way. In general, diester was the way to do it--no doubt about it at that time.

Gobind Khorana

Hughes: How much of a daily presence was Khorana?

Kleid: He was there every day, but he had a lot of people to tend to. We had lab meetings every week, and he would also have individual meetings with us. We would come in with our data and he would criticize how it was going.

Hughes: Was that intimidating?

Kleid: It was pretty intimidating. One of my experiments seemed perfectly okay to me, except the graph did not look smooth. There was some problem with the fraction collector in the middle of the night. In Khorana's publications I hadn't noticed that every figure was just perfectly symmetrical showing how nicely the oligonucleotide had come off the column. My graph line had this wiggly bumpy thing on the side--the graph line was not at all smooth. Dr. Khorana then explained to me that when he did this kind work he kept a cot in the lab so he could be there making sure everything went fine. I didn't understand that this result might not be so good. After I told Dr. Agarwal what had happened in my meeting. "You showed him that?! This bump--what's that? Oh, my god, you can't show him that! If he's going to publish this it's going to be embarrassing to him." All that had happened was that the fraction collector got a little stuck or something and that made the tubes not collect at exactly the right time. The result was a graph that wasn't smooth enough. I can tell you from then on my graphs looked a lot better.

Hughes: What is Khorana like as a personality?

Kleid: He was like a father to everyone in the lab--before I got there. It turns out that he is a professor beloved by dozens and dozens of his former students and many other people. But apparently a year or two before I joined the lab, the pressure of making this gene was very, very strong, and

he had a nervous breakdown. When I worked with him, he seemed to have a bit of a feeling of paranoia about him. He was not the kind of person you would ever want to go out and have a beer with. So that was kind of stressful. On seeing him about ten years later he seemed to me a completely different person. I imagine that the pressure to synthesize a gene and make it work had some impact on the way he acted.

Hughes: Yes, you caught him at a bad time.

Kleid: I guess. With the piece of DNA that I made, I had looked at the sequencing data before I started the project, and I didn't quite understand how they had gotten that particular sequence. Dr. Khorana assured me that this sequence was right. After spending about six months making this piece of DNA, Dr. Khorana explained to me personally that it turned out from more sequence data that the DNA I made was wrong. He said, "What would you like to do now?" (I kind-a wanted to do something different rather than go through that again.[1]) He just gave me a ticket to do anything in his lab. I chose to learn about DNA sequencing.

Collaborating with Tom Maniatis at Harvard

Kleid: The lab was divided into organic chemists and molecular biologists who did the sequencing. So I said, "I would like to do the molecular biology," even though at that time he would rarely allow his organic chemists to switch to molecular biology. I think there was only one other person that made the switch. If you were in organic chemistry you stayed organic chemistry--but he let me switch over.

The lab made another piece of DNA for another project that had to do with the lambda bacteriophage genes. I made part of this piece of DNA with the help of a couple of other postdocs, Drs. Yuri Berlin and Valery Smirnov from the Soviet Union who also became very good friends of mine. Then I did a sequencing project, sequencing a little bit of lambda phage.[2] That was very exciting. That was way more interesting than the organic chemistry. In a sense, "God" had now given us the tools to read our own code. It was very compelling.

At the same time, Dr. Mark Ptashne's lab at Harvard was working on the same project. Tom Maniatis was his postdoc. They happened to sequence the exact same piece of DNA that I

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[1]B. RamaMoorthy, R.G. Lees, D.G. Kleid, and H.G. Khorana, Total synthesis of the structural gene for the precursor of a tyrosine suppressor transfer RNA from *E. coli*, *J. Biol. Chem. 251*, 676-694 (1976).

[2]K.L Agarwal, Y.A. Berlin, D.G. Kleid, V.D. Smirnov, and H.G. Khorana, The synthesis of a DNA duplex corresponding to the icosa nucleotide sequence at the 5' end of the messenger RNA from the Gene N of bacteriophage lambda, *J. Biol. Chem.* 250, 5563-5573 (1975).

was working on.[1] So we decided to collaborate. The collaboration was that I would take that little piece of DNA, the one I was working on at Khorana's lab, and move over to Harvard. So I switched from Khorana's lab to Harvard with that project.

Hughes: With Khorana's blessing?

Kleid: With Khorana's blessing and Mark's blessing. I took the grant that I had gotten and moved it over to work with Ptashne. Then we did more sequencing, and we developed another couple of methods to do that.[2] We got deeper into molecular biology.

Hughes: What was the atmosphere of Ptashne's lab?

Kleid: It was completely different, as you might imagine. I moved to a lab that was mostly graduate students and one other postdoc, and that was Tom Maniatis. So we were the two postdocs and all the rest were very bright young graduate students. They were all struggling to learn everything there was to know about how proteins bind to DNA and what sequences they like--in particular, the lambda repressor and how the lambda repressor finds its piece of DNA, the lambda operator.

Early DNA Sequencing

Kleid: My job there was sequencing. I worked on the sequencing of all kinds of mutants of the lambda operator that interfered with the binding of the repressor so we could try to figure out what the repressor liked about that DNA sequence. So we sequenced these mutants, and as a result had a lot of theories on what was going on there.[3]

Hughes: Sequencing in those days was a very tedious procedure, was it not?

Kleid: It was.

Hughes: What was holding your attention, assuming that it was held?

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[1] D.G. Kleid, K.L. Agarwal, and H.G. Khorana, The nucleotide sequence in the promoter region of the gene N on the bacteriophage lambda, *J. Biol. Chem.* 250, 5574-5582 (1975). T. Maniatis, M. Ptashne, B.G. Barrell, J. Donelson, Sequence of a repressor-binding site in the DNA of bacteriophage lambda, *Nature* 250(465):394-7 (1974).

[2] T. Maniatis, A. Jeffrey, and D.G. Kleid. Nucleotide sequence of the rightward operator of phage lambda. *Proc. Natl. Acad. Sci. USA* 72, 1184-1188 (1975).

[3] T. Maniatis, M. Ptashne, K. Backman, D.G. Kleid, S. Flashman, A. Jeffrey, and R. Maurer. Sequences of repressor binding sites in the operators of bacteriophage lambda. *Cell* 5, 109-113 (1975). B. Meyer, D.G. Kleid, and M. Ptashne. The lambda repressor turns off transcription of its own gene. *Proc. Natl. Acad. Sci. USA* 72, 4785-4789 (1975).

Kleid: What was holding my attention was the data of course. Once you figured out the sequence, what was in there, what was the code? The genetic code concerns translation of RNA to make proteins. So what codon corresponds to which amino acid? But here we were looking at the code for promoters and operators, the sequences that start and stop transcription. We were looking at the next level of sequencing: What was in that DNA promoter sequence that RNA polymerase liked? It was the next level, and it was not that simple. Our group and Wally Gilbert's group and other people around the country sequenced a number of promoters and as a result we were starting to get a collection of sequences for these promoters. Then the simple idea was, well, just line them up and read the code now. But that was pretty difficult to do. The sequence data all by itself didn't give the answer, plus the sequencing itself was <u>way</u> more difficult at that time.

What we did was called the wandering spots sequencing method. You took a DNA and labeled it at one end and then you broke it down with chemicals so that it was either one, two, three, four, five, up to maybe twelve or fifteen nucleotides long. More commonly at that time we could start with a primer and elongate with one of the missing nucleotides, or a very small amount of it, so you got a whole population of DNA molecules that were from one or two to fifteen nucleotides longer than the original primer.

Then you would separate those by charge using electrophoresis, and then transfer that separation to cellulose, and then use another way to separate by size called homochromatography. You would see these little wandering spots going up the autoradiograph as the little piece of DNA got shorter and shorter. The longer stuff stuck on the bottom and made some spots, then the spots went up and to the left and right, and left and right, and up. I think one of my papers has a picture of those wandering spots.[1] It takes about two weeks to actually get some data. So you get fifteen nucleotides in a couple of weeks, and then you'd have to read it three or four times or get the sequencing data from both directions, to really figure out what the sequence was.

Hughes: Was this the Maxam-Gilbert method?

Kleid: No. That wandering spots method came before the Maxam-Gilbert method. When I came to Mark's lab I was working on this wandering spots sequencing method that was partially developed by Dr. Fred Sanger's laboratory in England and in Dr. Khorana's lab. Tom Maniatis was using it in his project before I joined Ptashne's group. We taught Alan Maxam, who worked with Wally Gilbert, how to use that method.

Actually, the wondering spots in a way led to the Maxam-Gilbert sequencing concept. One day another Russian, Andre Merzibekov, came to visit Wally Gilbert's lab and Mark's lab. The laboratories were just about right over each other on two floors in a building called the Harvard Biolabs. The labs held seminars together quite often. This Russian guy did chemistry on DNA molecules and noticed that you could break DNA molecules at G's [guanines] using a particular chemical called "DMS" and some other treatments. When radiolabeled at one end you could use that DNA in the wandering spots method if you did a partial reaction only

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[1]T. Maniatis, A. Jeffrey, and D.G. Kleid. Nucleotide sequence of the rightward operator of phage lambda. *Proc. Natl. Acad. Sci. USA* <u>72</u>, 1184-1188 (1975).

breaking the DNA at random sites to get a collection of different-length molecules. But if you instead ran a gel electrophoresis size separation, you could see a lot longer pieces and it looked sort of like a little ladder with rungs missing. Much like the wandering spots you would see a collection of molecules, but instead of spots you would see bands separated by a certain distance. That distance would be from the start of the molecule, the labeled end, to the first G, and go a little longer to the next rung, and that would be to the next G, and then a another rung would be the next G, and so on. So you could see this kind of ladder where spacing was dictated by where the G's were in the sequence. In the spaces would be where the As [adenines], Ts [thymines], and Cs [cytosines] are, if you could reveal those by some other treatment.

Alan and Wally said, "We could probably do that to the other letters. Maybe we can make a chemical that can break the chain at A's, and then maybe at C's and T's, and then run that side-by-side on a gel and see how that looks." And they did that. I still have a copy of the very first gel where they did Gs and Cs. Very soon after that we tried this in Mark's lab. In fact, I think one of the first few Maxam-Gilbert type sequencing gels published is in one of my papers.[1]

Alan Maxam was a good friend of mine. So I was there to see the whole DNA sequencing technology that broke through at that time. Dr. Frederick Sanger had a slightly different method. It was more like the wandering spots method with a gel. They used a primer but then did the elongation reaction four times using limiting amounts of G, A, T, or C and then ran them side-by-side together on a gel. The new conceptual thing with these new sequencing methods was really the gel, I think.

Going back to Khorana's lab for a second, I want to mention a few of other people that had an influence on me. One was Dr. Marvin Caruthers.[2] Like Kan Agarwal, who was the central figure or dominant scientist in the organic group, Marv Caruthers was a major figure in the molecular biology group. I think those were the two dominant scientists among quite a few

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[1]D.G. Kleid, Z. Humayun, A. Jeffrey, and M. Ptashne. Novel properties of a restriction endonuclease isolated from Haemophilus parahaemolyticus. *Proc. Natl. Acad. Sci. USA* 73, 293-297 (1976). [note: This paper contains a very good example of a dyslexic experiment. The plan was to treat the DNA with the restriction enzyme, label the ends, and then use the Maxam-Gilbert type sequencing method. Instead, I did the Maxam-Gilbert treatments first, then cut the DNA and labeled the ends. I figured, what the heck, it should still work. When I ran the sequencing gel it took me two days to figure out the crazy results I got. The restriction enzyme would not cut that population of the DNA fragments that had been treated with the DNA sequencing reagents if they reacted at the sites in the DNA sequence that the restriction enzyme required for activity. In this publication I repeated this dyslexic reverse experiment on purpose. In this study we proved that this particular restriction enzyme recognized a sequence quite far from where it cut. A few years later this technique was deemed "footprinting." D.J. Galas and A. Schmitz DNA footprinting: a simple method for the detection of protein-DNA binding specificity. *Nucleic Acids Res* 5, 3157-70 (1978).]

[2]In the early 1980s Dr. Caruthers helped start Amgen.

very, very ingenious people. Dr. Amos Panet[1] was one of those, and we did a project together with another Nobel prize winner, Dr. David Baltimore,[2] and the then postdoctoral fellow, Dr. William Haseltine.[3] [pause] So that was my career on the East Coast.

Hughes: A theme is that you were getting deeper and deeper into molecular biology.

Kleid: That's right. I was trying to help figure out how restriction enzymes cut DNA and how other proteins bind to DNA. My actual hands-on was always tied to DNA though, first trying to figure out how to make DNA, and then on to synthetic DNA, and then using primers in sequencing DNA. The last step was cloning DNA. It turned out that you needed those three steps in order to make genetic engineering into a practical technology; you needed to be able to synthesize DNA; you needed to be able to clone it; and then you needed to be able to see what you made.

Advent of Recombinant DNA

Herbert Boyer's Seminar at MIT

Hughes: Well, let's go to the cloning because in the period when you were a postdoc the Cohen and Boyer cloning papers were published. Do you have a story about that?

Kleid: Yes. I remember the first time I saw Herb Boyer. He gave a seminar at MIT, and he visited Khorana's lab and Malcolm Gefter and other people at MIT. He might have also given a separate seminar at Harvard or it was joint. MIT and Harvard were just down the street from each other, so often the seminars that had a major guy were attended by scientist from both.

Hughes: Do you remember which year? You were at Harvard 1974 to 1975.

Kleid: I was at MIT 1972 to mid-1974. What was the date that Herb went on his first tour?

Hughes: The first Boyer-Cohen paper was published in November, 1973. Boyer began talking about the work at least as early as the previous June because he mentioned it at the Gordon Conference on Nucleic Acids. The Singer-Soll letter arose from that conference which eventually led to

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[1]In the mid-1980s Dr. Panet helped Biotechnology General become a significant company.

[2]W. Haseltine, D.G. Kleid, A. Panet, E. Rothenberg, and D. Baltimore. Ordered transcription of RNA tumor virus genomes. *J. Mol. Biol.* 106, 109-131 (1976).

[3]In the 1990s Dr. Haseltine headed up Human Genome Sciences. We did several projects together during the 1970s including one with Dr. Gallo: M.S. Reitz, F. Wons-Staal, W.A. Haseltine, D.G. Kleid, C.D. Trainor, R.E. Gallagher, and R.C. Gallo. Gibbon Ape Leukemia Virus - Hall's Island: New Strain of GALV. *J. of Virology* 29, 395-400 (1979).

Asilomar and the recombinant DNA guidelines and all that. So it could have been in 1974 that Boyer gave a talk at MIT or Harvard.

Kleid: There was a controversy about it already, because I remember there were questions or something at the end about what the implications were. So it could have been after that Gordon conference.

Hughes: Controversy about the potential biohazards?

Kleid: Yes. A number of people were very nervous about cloning human fragments of DNA. I don't know who started the controversy, but I don't think in those days you could have given a talk without mentioning it--especially Boyer. He gave this talk which was basically about the Boyer and Cohen plasmid experiments.

Hughes: Was this a seminar or a larger gathering?

Kleid: It was just a seminar, but I think they got a bigger conference room. It was very highly attended.

Hughes: Boyer talked mainly about the science?

Kleid: Yes.

Hughes: Do you remember him saying anything about potential commercial application?

Kleid: No. It was about plasmids that you could use, and the selection markers, and how interrupting a marker could be useful. It wasn't pBR322 yet; it was pMB9, one of the earlier vectors. I'm not even positive if it was pMB9. But it was basically for *E. coli*, making plasmids, cutting the pieces of DNA, and showing you could create plasmids with different antibiotic markers.

Hughes: The audience was strictly scientists?

Kleid: Oh, yes.

The Controversy Over Possible Biohazard

Hughes: Were there any big names dissenting? I'm thinking of George Wald, the Nobel Prize winner, and his wife Ruth Hubbard. Were they already aware of recombinant DNA and attending seminars like this?

Kleid: They came slightly after, as I recall, because this was just the seeds of an issue. By 1975, when I was back in California again, the big controversy was when Wally Gilbert and Mark Ptashne decided they were going to need a special cloning lab at Harvard; they were going to do some of the experiments that Herb Boyer was talking about, and then they ran into this controversy. I think it was '76, '77 when those people came to the fore.

Exciting Scientific Possibilities

Kleid: In the very beginning it was all just very, very fascinating. I don't think anybody predicted that there would be any controversy because you were just talking about cutting and pasting DNA together.

Hughes: Were you excited about it?

Kleid: Oh, absolutely!

Hughes: Were the possibilities immediately apparent to you?

Kleid: The possibilities of learning more about how DNA works.

Studying Enzyme Restriction

Kleid: At Khorana's lab we studied restriction enzymes with synthetic DNA pieces. One of the other graduate students made a piece of DNA that happened to have a restriction site in it and reacted that with these restriction enzymes to see how they were working. One of those enzymes actually came from Herb Boyer, as I recall. I think it was EcoR1 that we studied even at that very early stage. Herb Boyer had known Dr. Khorana from before--I don't know how. Khorana was good about getting materials from different people and studying how they worked on DNA. This was exactly what Herb Boyer was interested in, how these enzymes functioned.

Hughes: Apparently Boyer was very generous about giving out his enzymes.

Kleid: Absolutely. And with his plasmids too. In fact, that started it all in my mind. Molecular biology at that time would not have been possible without a tremendous amount of cooperation between scientists, because you would trade your restriction enzyme or polymerase or ligase or plasmid so that you wouldn't have to make everything. It was a golden era of molecular biology.

Hughes: Did Stan Cohen enter into this exchange?

Kleid: I don't recall. Personally I didn't have that much contact with Stanley Cohen. I don't know why.

Hughes: Golden age of molecular biology--

Kleid: Yes, just like Gunther Stent's time. Only Gunther Stent missed it because he went into nematodes.

Reagent Exchange

Hughes: We're jumping ahead, I know, but that easy exchange of materials among scientists is not so easy anymore. Do you want to comment?

Kleid: But the exchange isn't as needed. Nowadays you can buy these enzymes and DNA at the DNA store. There are catalogues filled with all these enzymes. It's just a completely different issue. Back in the seventies you wanted to learn how this DNA is working: What are these promoters? What's causing them to be sites for RNA polymerase? How do these genes work? That was the issue. Plasmids were a new tool you needed in order to work on that. Think about Khorana's idea: let's synthesize the complete gene in the test tube and then see what happens. That was impossible then without a lot of help. It took thirty, forty postdoc years just to make the DNA, and then in using the assays to see if the DNA was any good--and then it was gone, used up in the tests. All of a sudden you could clone that DNA.

The first cloning of a synthetic DNA was with Herb Boyer working with Drs. Art Riggs and Saran Narang, (Dr. Narang was one of those former student-competitors of Khorana that we were talking about). They had synthesized the DNA that encoded the lac operator, and Art Riggs had spent his life studying the lac operator. So they made a synthetic DNA and then cloned it. Now you had enough so you could study how that DNA worked.

The Genentech/City of Hope Somatostatin Project

Hughes: Do you know how Riggs learned recombinant DNA technology? In those early days, how was the technology disseminated?

Kleid: In this particular instance, they all worked together. Dr. Narang made the DNA with one of his students, Dr. Itakura, and they brought that DNA to Art Riggs. Art Riggs was working with Herb Boyer, and so they made a plasmid with the help of Herb's group that included Drs. Herb Heyneker and Paco Bolivar.

Hughes: So that part of it was happening in Boyer's lab.

Kleid: Right. Boyer's lab and Art's lab. I think the cloning aspect was mostly in Boyer's lab, and it involved Herb Heyneker and Paco Bolivar and Ray Rodriguez. They were trying to develop a plasmid that was really handy for cloning that would have two markers. The ones that they chose eventually were for ampicillin and tetracycline. They constructed these plasmids so they weren't so unwieldy, because the original plasmids were very big and had lots of pieces when treated with restriction enzymes. So they whittled it down so it would be a lot easier to work with, and pBR322 by the late 1970s became the standard workhorse.

Plasmidology

Hughes: Was the Boyer lab the center of plasmid development? Were there other laboratories also trying to develop vectors?

Kleid: Not that I can recall. He wasn't really the center, but he was kind of the center from which the technology got disseminated. Just an example of what I mean: In Ptashne's lab when I was there there was a graduate student, Mr. Keith Bachman, who came to Boyer's lab in '74-75 and learned about the vectors and then took samples of them back to Mark's lab and started working on those same vectors at Harvard. That work was part of his Ph. D. thesis. He eventually became a postdoc in Herb Boyer's lab and even worked a bit with Genentech when it first started; he never actually worked at Genentech, instead he continued at U.C. Med Center. Anyway, Keith Bachman was, along with quite a few other postdocs, working on the next generation of plasmids after pBR322, so-called expression vectors. Others were working on vectors for other types of bacteria and yeast cells. But still, I would also say that Boyer's pBR322 got so widely disseminated and used (and it just worked perfectly) that it became such a standard that it was the end of the story. In a sense, *E. coli* cloning vector plasmid development was done in 1978. We still use it today.

Stanford Research Institute

The Job Hunt and Hiring Process

Kleid: So here I was at Harvard and it was really time to come home to California. I'd been trying to do that ever since I went to Pittsburgh. I had written for jobs and I had interviews at places like Syntex and a couple of other smaller companies on the West Coast.

Hughes: Why had you decided to go with a company rather than a job in academia?

Kleid: Academia has an awful lot to do with trying to raise money for your research. It just takes so much time and effort to try to do that particular part. And the universities were filled with molecular biologists. They had all they wanted because molecular biology was not that interesting to most of the universities at that time; it was just starting. They didn't have molecular biology departments; you were in organic chemistry or you were in biology. There was very little in the way of faculty positions in molecular biology except at the major schools, and they had their molecular biologists--and they were good. So, there weren't going to be any professorships out there for me, especially in northern California since I only had Berkeley to choose from, and I barely even graduated from there. I couldn't imagine being part of their department. [laughter] It was full of Nobel prize winners. They would look up my grades; that would be the end of it. So I thought that the industrial area would be a better fit--if "industrial molecular biology" only existed.

A Project on Anti-cancer Drugs

Kleid: I had written to Stanford Research Institute, SRI International now. I interviewed a person who worked there and that seemed like a really good fit for me because it was in between industry and academia. It wasn't an academic position, but you did research and you usually got your money from the government or from other companies. After my interview, I wrote a letter to them, and a year passed, and so I went and visited him again and really begged for a job.

Hughes: This was the head of SRI?

Kleid: No, this was the head of life sciences at SRI. His name was Dr. David Henry, and he worked more in organic chemistry. At the time he had a very large project on anthracyclines for cancer, the same ones we use now. He studied adriamycin and related anti-cancer drugs. These drugs work by binding to DNA and putting cells out of action by destroying the cells' ability to replication their DNA. So I felt there was a little fit there because I thought we should be studying DNA and this activity at the sequence level. I thought, well, nobody has really taken a look at how these anti-cancer drugs damage the DNA and change its sequence. Maybe we can take a look at that. I thought there would be some interest in that because the largest granting agency was the National Cancer Institute (or NCI), part of NIH.

I didn't think SRI was very much involved with molecular biology up to that point in time. Here was cancer and DNA and sequencing. So I convinced them that I could come up with some grant proposals doing that. So Dr. Henry said fine as long as I brought my grant with me. So I came with my grant. There was six or ten months of it left. I asked Mark Ptashne if I could take my grant to SRI. And he said it was okay. I guess it was up to $300 a month by then. So here I am, graduate student, Ph.D., three-year postdoc, and finally a real job--$300 a month, fine.

Mark Ptashne and Tom Maniatis

Hughes: Before you leave the East Coast give me a sketch of Ptashne.

Kleid: Mark was the youngest full professor at the time at Harvard, the youngest they had ever had in science. He is a very short guy. He had a little bit of a Napoleon complex. Some people have big egos and they're always telling you how wonderful they are. Well, his ego was so big he didn't have to tell you how wonderful he was because he knew you already knew it. [laughter] He was just an incredible person to work with.

Hughes: You mean incredibly good?

Kleid: Incredible. His lab was top-notch and people in there were extremely good. His vision of science was very, very interesting. He was trying to figure out how DNA works, starting with a very narrow little system, lambda operators and lambda repressors. He felt that that particular system was all you really needed to know about molecular biology. That was the only thing he

ever worked on from the seventies through the 1990s. I think he's at Sloan-Kettering now in New York City. But throughout his career at Harvard that was pretty much the only thing he ever worked on. He thought it was the most interesting thing to work on. He just really studied the details of the details in that little system. The more detailed your understanding the more questions would reveal themselves was his reasoning I guess.

His postdoc, Tom Maniatis, was one of the stars of the Harvard Biolabs. Everybody came to Tom for advice on how to do everything. Every new experiment they did, everybody migrated to Tom because he could explain to them very succinctly and very crisply, "Do this, this, and this." He gave them directions and off they'd go. He was a guru of the Biolabs. And in contrast here I was, the other postdoc, and I came from a chemistry background whereas Tom came from molecular biology. Tom had a huge following at Harvard, and my experiments didn't work that well, and I couldn't write that well.

One day Tom wasn't in his lab and somebody came in to get some advice. I was sitting there, and he asked a question. I happened to know the answer. So I was sitting in Tom's chair, writing the notes out for this guy, and Tom came in, and I was taking his place. This was really bad. I think from that time on he really didn't treat me that well.

On the other hand, I felt that Tom was such a dominant force, especially among Mark's graduate students, that they weren't actually learning to be scientists. They were leaning on him for every single thing, and they had been in Mark's lab for a long time. Some of them had been there for three or four years without even being close to finishing. So I was pretty happy when Tom moved on. And he was probably very happy to do that too. He went to Cold Spring Harbor, and then he went to Caltech, and then he ended up back at Harvard again. He's one of the main scientists there. He and Mark started up one of Genentech's competitors, in my mind a copy-cat company, Genetics Institute, now part of Wyeth.

Hughes: You certainly met high-profile scientists.

Interaction with UCSF and Stanford Scientists

Kleid: So I came to SRI. One of the first things I did was to look up Herb Boyer--well actually one of his postdocs, Herb Heyneker, whom I met in one of those scientific meetings. Some of my fellow scientists at SRI and I would every three or four weeks or so come up from Stanford Research Institute and go to seminars at UC Med Center. We did the same thing at Stanford. In fact, there got to be a little crew of us at SRI who would go to the seminars and be part of the academic community at Stanford and UC Med Center, so we weren't just isolated at SRI.

Hughes: Which seminars were you going to at Stanford?

Kleid: There was a professor there that we knew that would invite us to seminars. I haven't thought of these names in a long time.

Hughes: Do you remember the department?

Kleid: I think it was biochemistry. It could have been one of my friends from SRI knew somebody, and that's how we got started there.

Hughes: The biochemistry department at that time was a hotbed of activity on DNA.

Kleid: Absolutely.

Hughes: You were in the right place for DNA research. Did you realize when you went to SRI that you'd be where it was happening in terms of recombinant DNA?

Kleid: Yes. That was one of the reasons I wanted to come back here so much. My project was on DNA, and I was born and raised here. We interacted as much as possible with Stanford and UC Med Center.

Establishing a Laboratory at SRI

Hughes: Did you have to set up a laboratory at SRI?

Kleid: Right. My lab started out being about 20ft. x 40ft. long with one cleared bench with lots of drawers, all absolutely empty. "Here you go. Here's your lab."

Hughes: Did you find that intimidating?

Kleid: It was tricky because you had to start from scratch. SRI had places to buy some instruments and labware. There was also leftover labware. So I put together what I thought I needed. That early part of what I wanted to do was about chemicals binding to DNA and DNA sequencing, so I started off getting the original Maxam-Gilbert sequencing thing going.

Hughes: Were you on your own? Nineteen-seventy-five is when you arrived.

Kleid: Right. I was <u>completely</u> on my own. I was in Dave Henry's department where most of the people were organic chemists. They were working on anti-cancer drugs and analogs. So my area, DNA, was going to be completely new. One of the things I was going to do, and eventually did, was to clone some synthetic DNA's to be substrates for these chemicals because I wanted to have a little sequence that I knew exactly what it was. The idea was that we could take that little sequence, react it with the drug, put it into a plasmid, and then cause the plasmid to get replicated, and see how did it repair itself.

Biosafety Issues

Kleid: If you had a drug bound to it, the question was: How was it going to fix that? So I wanted to clone a known sequence of DNA. To do that, I needed to have a biosafety committee at SRI. It took a year to get permission to clone the lac operator.

Hughes: Did SRI have a biosafety committee?

Kleid: No, I had to start it. In order to do recombinant DNA under the NIH guidelines, your institution has to have a biosafety committee. I went to SRI's safety group that handles this sort of thing and we put together a biosafety committee and got members from inside and outside. Then one of the vice presidents at SRI--I don't recall his name--said in effect, "What are we doing this for? We don't want to do recombinant DNA; that could be dangerous. It's also controversial. We got into this kind of problem when we worked on chemicals involved with warfare" or something like that. In the Vietnam War era SRI worked on a project for the defense department, and there were marches and the protesters almost shut the place down. This guy says, "We don't want to do that again; we're going to have marches all over the place." We were just cloning the lac operator for crying out loud.

We eventually got the biosafety committee set up so I could do what I wanted to do. By that time I did get some grants to do it. I wrote a grant that went to the NIH granting agency and I tried to ask the kind of questions they were interested in. It just worked perfectly. I spent a lot of time on that.

Hughes: SRI must have been considered more academic than industrial, because, as you probably remember, the NIH guidelines only applied to academia.

Kleid: Or anybody working under an NIH government grant.

Hughes: Oh yes, that's right.

Kleid: If you wrote a grant that used recombinant DNA, you had to submit your plan to your own institution's biosafety committee. We had to jump through those hoops.

Hughes: Was it smooth sailing once the committee was organized?

Kleid: Once SRI management capitulated it was fine. The first biosafety committee was helpful in . that regard. But it wasn't warm and fuzzy.

Hughes: They were still nervous?

Kleid: The management was, but the biology section was perfectly happy. SRI wanted to get into this DNA area. The organization was, at that time anyway, a bit difficult. I always thought at the time, if you could make it at SRI, you could make it anywhere. You weren't going to have a guaranteed salary; it all came from grants--a total soft-money place. So you had to raise the money for your research--completely.

Hughes: You told me that one of the reasons you were interested in industry was so that you didn't have to write grants.

Kleid: I know. So here I am, spending all my time writing grants. And as I told you, I don't write very well. It takes me forever. Although they didn't have any word processing computers yet, they had a wonderful thing called editors. So I would do my best to scribble my stuff down and hand it to people who did know something about writing. They fixed it all up and typed it. I took advantage of that and wrote three or four or five grants while there. Once the grants were funded I was able to hire some fellows to help me.

Arrival of John Little and David Goeddel

Kleid: One of the postdoctoral students who came by asking about a job was John Little. John was from Stanford and I had met him there. He was a molecular biologist and he knew all about how to clone DNA using plasmids. I had been in the DNA part. I didn't do that much in actually cloning and looking for plaques and picking colonies. So he came to my lab and he worked on that part and I think did a fine job.

About six months or a year after John Little joined, I got a call from Marv Caruthers telling me that he had this graduate student, Dave Goeddel, who was just finishing his Ph.D.and wanted to come to California. Marv raved about how bright he was and what a good job he did as a graduate student. Dave wanted to come to California because it would be close to Yosemite. He was a rock climber first and a genius science student second. As a graduate student he did his projects extremely well. The University of Colorado has these rock formations right outside of Boulder. Dave spent a lot of time climbing these rock formations. He became an excellent rock climber. When he came to SRI his main goal was to have a job that was close enough that he could go to Yosemite whenever he wanted and climb rocks. So that's what happened.

While Dave worked at SRI he climbed El Capitan, and that's a one week thing. He explained to me how he does this: you have a rope, and you get a certain distance, and after about a day your rope doesn't reach the ground anymore, and you can't go back down. You have to go up. There's no way to go down. <u>You must complete the trip</u>. If you get nervous, your fingers sweat, you fall right off. So you have to be absolutely focused and confident and just climb that rock. It was just amazing to me that somebody could have a personality that would be interested in doing that.

Hughes: Did you ever see him do it?

Kleid: I went with him to the mountains a few times, and he did some rock climbing on big boulders. I didn't go to see him climb El Capitan or anything like that.

Dave was very talented at this and he had all the equipment. I recall that he told me that he met his future wife because she saw his picture on a poster in one of these climbing shops and said, "I want to meet that guy." She found him and she married him.

Hughes: Isn't that a story!

Kleid: Carol is her name. She was just like Dave, just totally committed to whatever they were going to do. It was amazing to see those two. They were so alike; they were like brother and sister.

Anyway, Dave came to my lab, and he learned the details of cloning: pouring the plates, transformation, growing of the colonies, picking colonies, and analyzing the DNA sequences.

Hughes: Which he hadn't done at Colorado?

Kleid: No. He was mostly on the DNA synthesis part. They did some biochemistry but not so much in cloning. At about the time Dave came to SRI, one of his former fellow graduate students, Eric Kawashima, synthesized the DNA encoding the lambda operator[1] While in Caruthers's laboratory Dave and another of Caruthers's graduate students, Dan Yansura, did the lac operator. Eric made the lambda operator DNA and he sent this DNA to us at SRI. Using the techniques that Dave had learned from John Little, we cloned the lambda operator. Our work on this has never been published. It was just before we came to Genentech near the end of '77. Dave was in my lab for about a year and he overlapped with John Little for about six months.

Hughes: In that year were you working closely together or was he doing his thing and you were doing yours?

Kleid: We had one lab. By this time the lab was outfitted pretty well. I had raised up a notch. I had gotten my grants, so SRI gave me a bigger room with nice benches and we just had them all painted. So we were in really good shape, with John Little and a technician too, so there was four of us. I did some experiments, but not really that much. I was still working on raising the money, writing the grants. I was not hands-on anywhere near as much as Dave. Dave and John had total time just to work in the lab and do experiments all day long. I really wanted to do the experiments, but they were having so much fun, they would hardly let me help.

At that stage Dave really had a good, solid knowledge of what to do, and he kept very good notes and nice directions.

Hughes: Was he working on DNA repair?

Kleid: That was the plan, but the first step was cloning the gene so we'd have a target, and we also did some studies on the binding of the drug. When the drug bound the DNA between the base pairs, it actually unwound the helix a bit. One of the interesting things that Dave Henry had worked on was two drugs hooked together. When you link together two chemicals that both bind to DNA and they bind extremely tightly. We were studying how those DNA binding drugs unwind the DNA. So we were doing experiments on that as well as cloning little pieces of DNA.

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[1]Kawashima, E., Gadek, T., Caruthers, H.M. *Biochemistry* 16, 4209-17 (1977).

II GENENTECH, INC.

The Somatostatin Project

Hearing about Somatostatin

Hughes: How did you hear about Genentech?

Kleid: Well, I told you that we used to go to all these seminars. One of the scientists I saw fairly often was Herb Heyneker. Herb and I, and his wife and my wife, became good friends. We went out with them a few times. Herb talked a bit about the somatostatin project that he was working on and how they made these DNAs. He was working with Art Riggs. That was really interesting. He was absolutely so excited about that. Then he talked about this Genentech company that they had formed and that company was funding this project. I went up to Herb Boyer's lab and visited with him a few times. As you can see our research was sort of along the same lines, at least it used some of the same techniques and tools. They were cloning synthetic DNA for somatostatin, and we were doing lambda operator. There weren't very many people in the world cloning synthetic pieces of DNA--there were almost none. So we had a lot in common. We needed the restriction enzymes too, and we needed other synthetic DNA pieces, so we were trading those around, because we hadn't actually made any DNA at SRI.

Richard Scheller's DNA Linkers

Kleid: One of the other people we met along the way was Richard Scheller. Scheller was making synthetic DNA's that had restriction sites in the middle.[1]

Hughes: He was at Caltech.

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[1]See the ROHO oral history with Dr. Scheller. [SSH]

Kleid: He was at Caltech, and he was also helping Genentech. He made little linkers that Heyneker was using in the lac operator project and might have wanted to use with the somatostatin DNA project. Previously they synthesized the lac operator and put linkers on the end. Those came from Richard Scheller. Scheller was going to synthesize the whole somatostatin DNA gene. Instead Keiichi Itakura took over and made those pieces. Scheller spent a lot of time making the very first somatostatin DNA piece and didn't quite finish it all. So it was just one DNA part and then another smaller DNA part, and then that could be joined together to make a little DNA with a restriction site. He made that, and then Art Riggs took those pieces of DNA up to Herb Boyer's lab and spent a lot of time learning cloning himself. That's how he got the hands-on experience with Heyneker.

Heyneker likes to tell the story of how Dr. Riggs cloned the *Bam* linker. Heyneker says, "Oh, that's all Art could do; he cloned the *Bam* linker." So later, with Dr. Itakura's DNA encoding the somatostatin, Herb Heyneker joined the pieces of DNA together, and with Paco Bolivar they were the ones that completed the cloning of somatostatin.

Hughes: Scheller is the name that drops out of most of the accounts. I noticed he's not on the somatostatin paper. Contributing the linkers isn't enough to make you an author? Of course he was a graduate student.

Kleid: He was a graduate student. He got thanked for those pieces of DNA and he is on the paper describing the original use of the linker. He had given the linker out to a lot of people. What he used to do was to have a piece of filter paper and squirt a little sample of the linker on it and mail it to you. So he got on a lot of papers by doing that, mostly being in the thank-you section.

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Kleid: The somatostatin gene was designed with *Eco*R1 restriction site on one end and *Bam* on the other, so in the final plan they didn't use the linkers on the somatostatin project. But if you look at the lac operator cloning project, the one that came before, that one used linkers.

Hughes: I, maybe wrongly, associate Scheller with the somatostatin project.

Kleid: He made one or two of the pieces of DNA that they were going to use to do somatostatin, but those pieces of DNA didn't work.

Hughes: Why?

Kleid: Turn off the tape recorder and I'll show you. [tape interruption] I happen to have Richard Scheller's notebook from Caltech here in my office because we were using this in a litigation about ten or fifteen years ago and we actually never gave it back to him. [laughter]

Hughes: Now it comes out.

Kleid: I had fished it out because I was going to give it back to him a couple weeks ago. This has his first experiments from 1975 all the way through to him making the piece of somatostatin DNA. I'm sure that he'll be interested in seeing this again.

New Emphasis on Keeping Notebooks

Hughes: That notebook of course comes from the period when he was a graduate student at Caltech.

Kleid: Right. He wasn't that good at writing his name and date on the pages here.

Hughes: That's significant, isn't it? The notebook dates from a time before people were so conscious of intellectual property claims.

Kleid: Right, they weren't conscious of it at all then, and they still don't do this very well. [laughter]

Hughes: Say you as a patent agent.

Kleid: I have looked though enough notebooks, especially those from Genentech, where the directions for how to keep a notebook properly are right in front of the book. How many people actually keep a good record? Not many. I happen to have my own 1978 notebook right here too and you can see the absolute opposite. [chuckles]

More on Early DNA Synthesis

The Diester and Triester Methods

Kleid: Anyway, back to the Richard Scheller story. He synthesized these synthetic DNA's. I met him on one of his trips up here to see Herb Boyer's lab. Anyway, this was just kind of cross-fertilizing that happened in Boyer's laboratory. The very few people that did cloning of synthetic DNA molecules at the time all got to know each other.

Hughes: There were the people that Khorana had attracted, weren't there?

Kleid: They came there too. Dr. Khorana's lab did an experiment on the cloning of the transfer RNA that was being made while I was at Khorana's lab in the early seventies. In the late seventies, after the lac operator was cloned, they decided to go ahead and clone the DNA that they made.[1] I don't think it was the original concept to do this because, as I said, the concept was to chemically synthesize the DNA and show that synthesized DNA worked in the test tube.[2] But

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[1]Brown EL, Belagaje R, Ryan MJ, Khorana HG. Chemical synthesis and cloning of a tyrosine tRNA gene. *Methods Enzymol.* 1979;68:109-51.

[2]Khorana HG, Agarwal KL, Besmer P, Buchi H, Caruthers MH, Cashion PJ, Fridkin M, Jay E, Kleppe K, Kleppe R, Kumar A, Loewen PC, Miller RC, Minamoto K, Panet A, RajBhandary UL, Ramamoorthy B, Sekiya T, Takeya T, van de Sande JH. Total synthesis of the structural gene for the

here with cloned DNA, you were using biology to replicate it. In Khorana's eyes it might seem to be kind of a cop-out; you're not really using the chemistry anymore. But let's go ahead and clone it. And they did, and they ended up learning a lot about that particular DNA and how it works by going ahead and studying the cloning of it. They cloned the DNA molecules that were made by the diester method. That's the big difference between Itakura-Narang-type DNA used by Dr. Rigg's which was made using the triester method.

Now the trouble with the triester-made DNA is that it's not very pure; it's slightly damaged by the chemical treatments. But it didn't really matter because if you're going to clone it, the biology selects out the DNA that's just right. So even though maybe only one in a hundred of the joined DNA molecules will be perfectly okay, that will be the one you clone. So it just really made it all possible because now you could make the DNA really quickly.

Hughes: Had Khorana considered the triester method but rejected it because it wasn't as accurate?

Kleid: That's right. They always had a small group not only synthesizing DNA but also developing new methods. They definitely did all the studies on the triester approach, the pros and cons of it, and as far as what Khorana wanted to do, it was not going to be useful.

Hughes: Why did Itakura take that route? Didn't he start working on synthetic DNA before recombinant DNA came along?

Kleid: Right. Like Narang whom I met a few times. He was from Canada and he was making DNA using this triester approach because he wanted to purify the DNA on silica gel. That's very quick, whereas we had to purify it on cellulose, which took a week; the columns took a week or two to run.

Hughes: Because the molecules were so big?

Kleid: They were big and sticky, and the way that this column worked with a gradient, it just took forever.

Hughes: So Narang was trying to speed up the process.

Kleid: He was trying to speed it up. When you use it with the silica gel, you could do the thing in a day, so that was really taking a lot of time off. The reason he could do that was the phosphates were all blocked, so the DNA molecule was acting more like a lipophilic chemical rather than a diester where every single molecule has a charge at a particular pH. You were separating the molecules by charge, so you could really do a nice job in separating them because you could see a two and a three and a four plus charge each come out separately on this column. It took a long time but it was very, very elegant; whereas this triester was not elegant and was not clean, but it was fast.

Hughes: Was speed mainly why Itakura was using the triester approach?

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precursor of a tyrosine suppressor transfer RNA from *Escherichia coli*. 1. General introduction. *J Biol Chem*. 251(3):565-70 (1976).

Kleid: It was. You could actually make the DNA in a reasonable time. As I said, for this one gene, the piece of DNA that I worked on was six months of labor for one piece of DNA.

Hughes: Was it serendipity that Itakura got linked up with Herb Boyer and the recombinant DNA business? I mean, he didn't choose the triester method thinking, "I don't have to worry much about the purity of this approach because I'm going to clone the DNA."

Kleid: Exactly. It is very much serendipity. Art Riggs at City of Hope wanted to make the lac operator and study it chemically, so he linked up with this young graduate student, Keiichi Itakura. Art was very impressed with his ability so he brought him to City of Hope. Dr. Itakura worked at Caltech for a time. Then Riggs got Itakura started at a lab at the City of Hope doing this. Itakura's first student co-worker was Scheller. They worked together at Caltech. They started using the chemistry to make DNA molecules called the triester approach. As I said, there was just very little interest in the whole United States, anywhere, in making DNA; so this was really an outpost.

The methodology that they chose, the triester approach, is what Itakura developed as a student. He thought it worked really well. I think he had more impact on the development of this than his mentor, Dr. Narang. At scientific meetings during this time, Dr. Narang talked about Itakura--and another Japanese scientist who worked with him--and how many hours and hours they would spend in the lab, what terrific scientists they were, and how dedicated they were to making this work.

So Narang and Itakura were perfectly happy with the quality of the DNA from the triester chemistry. Even though it wouldn't satisfy Khorana's group, it would certainly satisfy them. There's no question in my mind, they weren't really thinking about how the triester method would be okay for cloning. It was much faster, and it turned out that it was just the perfect thing. We didn't really need the DNA to be super pure; the bacteria would take care of it.

Courted by Boyer and Swanson

[Interview 2: November 29, 2001] ##

Hughes: Please start by telling me the reason, or maybe the reasons, that you decided to give up a secure job at SRI and start in with this new and unknown company Genentech.

Kleid: As I recall, the start was a phone call from Herb Boyer, who, as we mentioned, Herb Heyneker worked with as a postdoctoral fellow. Herb Heyneker was a good friend of mine over the last five or six years. We're talking about the end of 1977?

Hughes: Probably, because you started at Genentech in '78.

Kleid: So I think it was December of '77 Herb Boyer gave me a call and mentioned that he was talking to Herb Heyneker about the work I was doing and wanted to invite me out to dinner. So I agreed to do that. I went to San Francisco and met with Herb Boyer and Bob Swanson at a

French restaurant in San Francisco. We had a very lovely dinner. They told me about this Genentech company that they started. At that time the company had no location, and they told me that now they wanted to have an actual facility with employees and everything.

Hughes: Had you met Herb Boyer before?

Kleid: I had been to his lab a number of times. We used to go to seminars at UC Med Center, and I had been in his lab. I may have been introduced to him, but I actually can't recall that now. The first time I really had a conversation with him was at that dinner.

Hughes: How did the conversation go?

Kleid: Well, they described to me that they had started this company, Genentech, and they felt it was time to move into their own facilities. They explained to me what they had been doing at UC and at City of Hope on the insulin project. They said it was time for them to build a place, and they would like me to be part of it. I came to that dinner with the idea that Dave Goeddel and I were interested in making DNA molecules, and maybe we could work with them. We could help synthesize some other genes they might be interested in downstream, so that was my mind set.

Hughes: Meaning that you would stay at SRI?

Kleid: Right. Because I hadn't heard anything about them wanting to start a company with a physical location; I thought that they were supporting research in universities. So it was pretty much a surprise to me that they wanted to actually start a place. They said that Herb Heyneker was going to come. They didn't know where the facilities were going to be at that point, but they wanted to see if I'd be interested or not.

So we talked a lot about their capabilities, because the first thing I was afraid of was, this is a commercial venture to do DNA, and as far as I knew no company had ever before been involved with that sort of thing. But they said that they had contracts with companies that they were going to enter into or just about to enter into--I don't think they were very clear on whether they had entered into them or were going to--and that they had venture capital funding. At any rate, I was very impressed with that because at SRI, as I said, we spent a lot of time trying to get money to support our research. SRI really loved money from companies rather than the government because with companies they could charge a bit more for overhead. But those corporate funds were virtually impossible to get because most companies are very, very tight with their research money and watch over it very carefully, and to give research money to somebody else is something they don't like to do. But here Herb and Bob were saying, "Oh, we're going to get all this money from these companies." So whoa!

Recruitment for the Human Insulin Project

Kleid: So all right, "What is the project about? How far are we on the project?" We had heard that they were doing insulin, and they described to me that Paco Bolivar had been working with Art

Riggs doing the cloning of synthetic DNA for the insulin B-chain. They said they had made some progress cloning the insulin B-chain but they wanted to finish it right away. The DNA was made, and Bolivar couldn't spend as much time there as they had hoped. He had gone back to Mexico, and so the project was sitting there and they needed somebody to work on it. I had assumed that they were further along than that. So now all of a sudden there was a bit of work there, and Dave Goeddel and I really knew how to do that particular kind of thing. There weren't many other people in the world that had done that kind of work.

Hughes: You mean DNA synthesis?

Kleid: Well, the synthesis was finished , but cloning synthetic DNA.

Hughes: So they wanted you as cloners.

Kleid: They wanted us as cloners. The DNA was made, sitting there, and needed to be hooked up, cloned, sequenced, and then expressed to make the insulin.

Hughes: There was nobody available in Boyer's lab? They were tied up with their own projects?

Kleid: I don't know what the situation was.

Hughes: It could have been more complicated than that.

Kleid: Well, I know the idea of going to start their own company meant they wanted to move the work from inside the lab into a company, and maybe Herb Boyer's postdocs and graduate students didn't want to do that. Or maybe Herb wanted to keep them on his research projects; he didn't want to decimate his lab, and he wanted to find people that were interested in doing something in companies rather than in academia.

Hughes: Boyer was under fire by 1978 because of the blending of the academic and the company business. So another factor may have been wanting to separate the two activities.

Kleid: That could very well be, because it would be quite a switch: the paycheck would come from a company, not grant money given to the university. Also, this project has a subtle difference: in academia you're trying to discover what mother nature knows; you're kind of approaching the truth as mother nature taught it. The goal is to understand completely, but you never actually get there. The closer you get the more questions you find. Its like going up a learning curve that looks like an asymptote. Whereas in a company you have an idea of what you want to do, and you want to make it happen. There is a target. Physically "doing the work" is actually not that different. But the ultimate goal is kind of different, because in academia no matter what you find from nature you've made progress, and you can publish it. But in industry if you don't get this thing to work you have wasted a lot of time and money, and who knows what happens to you next! So it's a different mind set. But Boyer's and Swanson's idea was pretty attractive: "Let's figure out how to make human insulin."

Kleid and Goeddel Join Genentech

Kleid: Herb Boyer's a friend of Dave Goeddel, and they have different stories as to what happened next after that dinner. It must have been on a Friday. I immediately talked to Dave Goeddel about that dinner, and I remember it was on the phone, so it was probably the next day.

Hughes: Had you mentioned Dave to Herb and Bob?

Kleid: It was like the final thing I had mentioned. I said, "I have this postdoc, Dave Goeddel, and I'm not coming without him." And they said, "Oh, we want both." [chuckles] "If you're going to do this, we want both. That's no problem."

Hughes: That was their answer because at that point they really wanted you?

Kleid: They had never heard of Dave before. They wanted <u>anybody</u> that could do this stuff.. But, no one admitted that. They knew I had the capability to do what they wanted. We talked about that. I don't know if they realized <u>how</u> close we were to knowing the technology that they were trying to do.

Hughes: How had they learned about you and what you were able to do?

Kleid: From Herb Heyneker.

Hughes: Oh, that's right.

Kleid: Herb had been to my lab so he knew that we were interested in cloning synthetic DNA and seeing if we could make products out of plasmids. He knew that we knew how to do that, and we might be interested in making this jump. So I told them that I had this postdoc, Dave Goeddel, and I said, "I have no clue at this point if we will come." I needed to soak it in a little bit. I talked to Dave the next day and told him what I had learned, and I could tell right away that he was very interested.

I told you that the reason Dave came to work for me is that he wanted to climb El Capitan and spend his time rock climbing, and that was very apparent in our interaction at SRI. He's a very hard worker, but he was really interested in rock climbing. If we did this project at Genentech, he had to really want to do that. That was important--I didn't want him to be just following along. This would be a huge commitment. I felt that if he was really interested then that would be great. Rather than I make the decision, I said, "Dave, if you want to do it, let's do it." He was game right away.

Hughes: It was the insulin project that was attractive to him?

Kleid: That's right. I explained to him where they were in this project, and that they had the synthetic DNA but they needed to clone it. He was doing that same exact project on lambda operators. It was quite clear that he knew exactly what to do technically. We didn't need anybody to tell us <u>how</u> to do this stuff. We knew how to do everything. All we needed to do was to put a lab together and do it. But Genentech had no place at that time.

So the next week, probably right away, I called back Bob Swanson and told him that we were definitely interested, and that this project seemed like something we've got to start on right now, because if you sat on something like this we were going to get beaten out. I don't know exactly how I put it, but I said something like, "Look, if we're going to do this, we're going to do this right now. We've got to get going."

<u>The Competition on Insulin at UC and Harvard</u>

Hughes: Were both you and Swanson aware of the players in this area, that there were some pretty competitive people?

Kleid: We were certainly aware of the work of Axel Ullrich and Goodman at UC, which was the cDNA approach. They had done rat insulin. I don't know if we were aware at that particular time that Wally Gilbert had made a commitment to do this. I actually think that this may have been a slightly bit later but I'm not sure of the timing of that.

Hughes: He was doing insulin at least by '78.

Kleid: I didn't know about that.

Hughes: An article in *The Wall Street Journal* announcing Gilbert's work on rat insulin is dated June, 1978.[1]

Kleid: I don't think I knew about this in February 1978. I remember this [work of Gilbert's team] being in the summer of '78, right in the middle when we're working with insulin. We had a gene that we could hook up now--we'll get to that--whereas this one here of Goodman's and Gilbert's was just the cDNA. What are you going to do with this?

Hughes: I diverted you. Let's proceed more systematically.

Kleid: As I said, I told Bob we were interested, but I also said, "Look, if we're going to do this, we need to do this right away. We are prepared to start right now." So Bob came down and visited Dave and me at our lab and met Dave for the first time. Up to this time Herb Boyer had never met Dave; he was just a postdoc. But I knew he was a special one, and I wasn't going anywhere without him.

Today, every time I see Tiger Woods I think of Dave Goeddel. There's something about the way he approaches things--he's concentrating so hard, every single shot that Tiger Woods is going to take is going to be the best shot he's ever made in his life. You can kind of see that. And if it goes right, you see this huge smile, and if it doesn't go right, oh, there's just a lot of anger. But when he gets to the ball, the anger is gone, even if the ball's in the woods

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[1]Jerry E. Bishop, "Scientists Use Bacteria to Produce Insulin in Step Toward Better Care for Diabetics," *Wall Street Journal*, June 12, 1978. [SSH]

somewhere, and the next shot is going to be the best he ever shot in his life. That's the way Dave is. An intensity that you see mostly in sports was being applied to doing experiments in the lab.

Hughes: How was that for you as a colleague?

Kleid: Well, fine. I mean, we were partners. What better partner would you like? Yes, I thought it was great.

Genentech's Physical Setting and Development

Kleid: So Bob said, "All right, we will move on this," and he proceeded to find a place to start Genentech. In the next couple of weeks he secured to rent a corner of an airfreight warehouse building on the corner of what is now DNA Way and Forbes at Oyster Point in South San Francisco.

Hughes: Because it was cheap? Was that why Genentech ended up in South San Francisco?

Kleid: I think there were a lot of features of this particular location that they liked. One, it looked pretty nice. It was near the water; the building was fairly new. It had the possibility of expanding. Even in those days when Bob rented the first little corner, he looked at this long building, which was just an airfreight warehouse and said, "Look, we can expand and keep going down the length of the building, so we can do everything here." Then he looked at this little place and said, "This will be a great campus someday."

Hughes: You really think he had that vision--he was already thinking of a campus?

Kleid: Yes, he was. I can tell you that's what he told me a few months later when we actually got here.

Early Employees

Kleid: Then he hired a secretary, Sharon Carlock, and a guy named Brian Sheehan who was from Squibb. He was a fermenter operator who was interested in business. Dave and I said, "All right, we'll join." So he hired us too.

Hughes: Wasn't Swanson jumping the gun by hiring a fermentation expert before Genentech had a scientist?

Kleid: I'll say! Now he wasn't just a fermenter operator anymore; he was now the "Vice President of Manufacturing." [chuckles]

Hughes: Was this for show to the potential investors?

Kleid: I don't know what Bob was thinking. Sheehan found work to do. He helped get the labs going and he found a fermenter to buy. Yes, by the summer of 1978 he had bought a fermenter from Eli Lilly and Company that they didn't want anymore and had it hauled out to Genentech and set it up and spent about a year trying to get the darn thing to work. It was a fancy gadget. It had about sixty-liter and ten-liter tanks as part of it. We used it a few times. He said he got it for ten cents on the dollar. So he was committed to this: "You give me the bugs and I'll make the product." I would kind of roll my eyes because there are another couple of steps there.

Hughes: Do you think that Bob and Sheehan were still thinking that somatostatin might be a product?

Kleid: Well, it was definitely something that they could try and make if we had time to work on it. The clinical use of somatostatin had not been established, and so you'd have to figure out what to use it for. Maybe it would be used for acromeglia, too much growth hormone. It reduces the amount of growth hormone. So there really wasn't much of a potential market for somatostatin.

Hughes: I was looking for a reason why a fermentation capacity would be introduced into Genentech so quickly. I thought that maybe somatostatin was originally thought of as not only a proof-of-principle project but also a potential product. But from what you're saying, it doesn't sound that way.

Kleid: We really weren't thinking about that, and the effort to go into that would have been a lot, and it would have taken away from insulin.

Hughes: You were saying to Bob, "If we're going to be in the insulin business, we've got to get going right now." If you hadn't come along, would he have taken a more leisurely approach to making Genentech a physical company, finding lab space, etcetera?

Kleid: My impression was that he was slightly frustrated with the progress that Paco Bolivar and Art Riggs were making and didn't want to depend on them anymore. I think I was one of the early scientists that he and Boyer approached. They also approached Axel Ullrich and Peter Seeburg at this time or slightly earlier, and that didn't pan out.

Hughes: They were waffling about joining Genentech?

Kleid: Yes, they were academic scientists. They didn't really think about doing this, plus they had jobs that they really wanted to keep. Swanson and Boyer couldn't convince them to do it. If Dave and I hadn't done it, Bob would have continued looking with Herb Heyneker's help.

Hughes: What I'm trying to get at is, was it you that put the fire under Swanson? Did Bob, when you first met him, realize how competitive the insulin field was, and that if Genentech was going to do it, they had to get right on to it? Or were you the one?

Kleid: I don't think I can take credit for putting a fire under Bob. [laughter] Maybe I caught the fire from him. There was an urgency on his part, and I said, "Well, if you're going to hire us to do this, and we are available now, we want to get started right away." That also, in a sense, would close him off him from looking for other people--right? "We're going to hire two people now;

let's do it." So it would be Dave and I really taking the project in our hands: "We're going to do it now." That would be more like my motivation. This was a really good opportunity. So we decided we were going to grab that opportunity and see what happened.

Kleid's Initial Doubts about the Insulin Project

Kleid: My feeling was that this insulin project was incredibly chancy, and that my talking with Bob and Herb as to what they thought was needed at the commercial end was incredibly naive. My general feeling was, "This is very naive of them to think that they can actually do this." Then as we joined my feelings were confirmed even more.

Hughes: What were the factors that made you think they were naive?

Kleid: The first thing was the data on somatostatin. How they made the somatostatin! It was just a little tiny peptide on the end of 1006 amino acids of β-galactosidase. Then the process to isolate that and purify that--you could only demonstrate that it was there--that is not a product.

Now the plan with the insulin was to copy the somatostatin: Let's put the A-chain and the B-chain on the end of the 1006 amino acids, grow these bacteria, isolate that, cleave it off, purify the A-chain, then do the same thing with the B-chain. Then assemble them together and prove that you have made insulin.

Hughes: Did you talk in detail at that first meeting about how you might assemble the A- and B-chains?

Kleid: I don't know if that particular part was discussed, but the idea was that the somatostatin experiment was out there and how it was done. So we could use that method to make insulin.

Hughes: That was the model.

Kleid: Herb Heyneker had given a talk [on somatostatin], so we knew exactly how they were going to do that, and Bob said, "We're going to just do the same thing for insulin."

A little later we talked to Art Riggs about putting the two chains together, and it turned out that he was already studying that. He had gotten some insulin and separated the chains and was learning the chemistry of oxidizing the two chains back together. There was a procedure by Dr. A. Katsoyannis. Katsoyannis had developed a way to put the A-chain and the B-chain together. The yield was 10 or 15 percent, which seemed high to me because these chains polymerize with each other. Art had worked on that method, and so we were feeling pretty confident that we were going to be able to demonstrate the presence of insulin if we got it made. I think I was pretty confident about that. So we proceeded to do that.

SRI's Lack of Commitment to DNA Research

Kleid: The first thing I did was say to SRI that Dave Goeddel and I were going to leave to join this company.

Hughes: What was SRI's reaction?

Kleid: The reaction was, "Okay." It turned out that the guy who hired me at SRI, Dave Henry, had moved on to another company. I described to you that we spent a lot of time trying to get the biosafety committee going, and one of the VPs said, "What are we doing recombinant DNA work at SRI for? It's going to be the war-protestor thing again. We don't want to do that." But we got through all that and it took a lot of effort not only by me but by vice presidents at SRI. So they were not that excited about doing this DNA work I would say. They were lukewarm about doing it in the first place.

Goeddel Sets Up A Lab at Genentech

Kleid: Then I said, "Bob, why don't we get Dave going right away? I will stay here at SRI a little longer and hire some people to take over my grants." We had just gotten them a year before. SRI would be happy to keep going with that research. So I hired a couple of scientists to replace Dave and me. Dave came to Genentech, to the warehouse, and started ordering the glassware and things like that. The lab itself was absolutely empty. We're talking the four walls, the ceiling, and the floor. That was it. That was actually the same situation at SRI when I came there three years before. We're doing it again. So this time I'll let Dave do that.

So Dave would come up to what was to be Genentech and go through the catalogues and order the glassware and things we needed. Brian Sheehan and Bob arranged to buy lab benches. They were just benches with no drawers. They outfitted a room, 40 ft. x 30 ft., or something like that--a bench on each side and one down the middle. They ordered a fume hood because some of the experiments were going to require chemistry. So the benches and the glassware started arriving. We're talking about from March 1978, when Dave started, until June before we actually physically moved in. March, April, May, June--it took four months.

The Human Insulin Project

Work at the City of Hope Medical Center

Kleid: During that period we commuted to Los Angeles to Art Riggs' lab. Outside his lab were places where people visiting the City of Hope Hospital would stay while their relatives were ill.

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Kleid: Where we slept was very spartan, but it was very close to the lab, so we could do the experiments.

Hughes: Both you and Dave went down at the same time?

Kleid: Right. April 1st was our first trip down there. I had some vacation time coming, and I agreed to be a consultant at SRI for a few months while we were hiring new people and getting them started. So I had a part-time job there. My start date at Genentech was April 15th or so. So I went to City of Hope a couple of weeks before I actually started full-time at Genentech.

The Science

Kleid: We started down at City of Hope, and we got the synthetic DNA molecules and did the experiment where we mixed together all the different DNA molecules and joined them. The synthetic DNA paper has the picture of the gene.[1] Eight or so oligonucleotides were put in a test tube all together, and some of them were phosphorylated. In one test tube would be all these different oligonucleotides, and you would warm up the sample and then slowly cool it down, and these little synthetic DNA's would assemble themselves into a little helix. Then you could join them together with an enzyme called ligase, which joins the different pieces together, and make a teeny tiny synthetic gene. It was all set up. Once that joining was done you could isolate the synthetic gene on gels. In this case they were polyacrylamide gels of fairly high polymerization, 20 percent or something like that.

You would put this little mixture of DNA on a gel, and after autoradiography you could see bands indicating the range of molecular sizes. If there were little tiny helixes that hadn't joined together, they would run fast, and then going up the gel they would run slower and slower until you got the size you wanted. We knew approximately what size we wanted. Then the idea was to cut out that little piece of polyacrylamide gel with the DNA in it, and soak it out of the gel, and then add it to the cloning vector plasmid. We then annealed it to a plasmid, again by warming and cooling, and added ligase to join the DNA together.

Every once in a while you would have the gene assembled correctly within the plasmid. So you'd have the plasmid and the little synthetic DNA was joined to it by the ligase. Again, ligase joins DNA together. It keeps joining and joining and joining until there are no more ends. That's all it knows: There's an end. So what you end up with is a polymer of everything. But every once in a while you'll get a circle with your little gene in it. What we did was have a plasmid cloning vector that was cut open with two different restriction enzymes. A plasmid can have two different restriction sites that don't go together very well. Then the synthetic gene will match up, so it will have those restriction sites recreated, so that you will make a circle with your little gene on it.

Hughes: What ratio of plasmids with and without synthetic DNA was there in those early experiments?

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[1] Roberto Crea, Adam Kraszewski, Tadaaki Hirose, and Keiichi Itakura, "Chemical Synthesis of Genes for Human Insulin," *Proceedings of the National Academy of Sciences* 1978, 75:5765-69. [SSH]

Kleid: It was fantastically small, probably one in a couple billion. But the beauty of cloning is, you take this mixture, and you put it into bacteria, and every once in a while one of these correct plasmids will go inside the bacteria. If you're really, really lucky the bacteria will take up the one DNA vector with the insert you want. Then you grow them up. What happens is most of the bacteria don't have any vectors in them. Every once in a while there's one that has plasmids. Only the ones that have a cloning vector in them will grow against the culture medium background because you put an antibiotic in the petri plate. It kills off all the bacteria that don't have a plasmid.

So now you have colonies growing up that have plasmids. But how many of those have your gene? Is it wrong, backwards, whatever, or did the plasmid just close up? What we would do would be in steps: isolate the gene polyacrylamide gel, link it to the plasmid, transform the plasmid into bacteria, grow the bacteria up, look at the bacteria and see if there's any with a DNA insert of the size that we wanted. We would pick each individual colony that grew up, make a little culture out of it, then break it open and see if the plasmid we wanted was inside. We knew how long the DNA was, what the restriction enzymes sites were, so we'd cut it out and look at its size on the polyacrylamide gel again. Now we should find a nice clean band of the size we were looking for.

Hughes: You cut it and put it on a gel again?

Kleid: Back on the gel so you could compare it to what you started with--a smear of stuff. And now you maybe had exactly what you wanted. You had to search through a dozens of these bacteria with plasmid inserts to find the ones that were right.

Problems with the B-Chain

Kleid: It turned out our friend Paco Bolivar had done half of the B-chain. The two parts of the B-chain gene are shown in the diagram in our publication.[1] He had done the part that we called B-H in the figure. It has an *Eco*RI and *Hind*III restrictions sites on the ends of it. Then Dave and I worked on the other part called the B-B, it has *Hind*III and *Bam*HI restrictions sites. Paco was unable to clone the DNA encoding the B-B, he just couldn't get that one to work. Dave and I also cloned the DNA encoding the A-chain.

Hughes: You mean Paco couldn't clone the B-B DNA?

Kleid: That's right. So Dave and I worked on the B-B. We got the A-chain to work fine. But like Paco, we also were not able to clone a synthetic B-B gene. We really only needed to find one gene. Even though we started off with quadrillions of genes and plasmids, in the bacteria we're going to get a single plasmid and that's going to replicate itself and make a whole bunch of

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[1]D.V. Goeddel, D.G. Kleid, F. Bolivar, H.L. Heyneker, D.G. Yansura, R. Crea, T. Hirose, R. Kraszewski, K. Itakura, and A.D. Riggs. Expression in *E. coli* of chemically synthesized genes for human insulin. *Proc. Natl. Acad. Sci. USA 76*, 106-110 (1979).

copies of itself. So all we needed to do is get one right. We were talking about the Khorana research where they were trying to make a functional gene in a test tube. Here we just needed one gene.

For the B-chain, after looking through lots and lots of plasmids, there weren't any that were correct in size. We looked through more and more and more, and we couldn't find one with the the B-B part of the B-chain.

Hughes: Were you lucky with A and unlucky with B, or were you very, very lucky with A to get it so quickly?

Kleid: I would say that we were fortunate to get the A and very proud of our accomplishment. The fact that we couldn't get the B-B, we were borderline embarrassed. How could we not do this? So we had to try it again. Frankly, we were shocked that we couldn't find any at all. It was a lot of work at this point. What we resorted to was scaling it up. We said, "Let's just do the whole thing ten times bigger. We'll really just take a sledgehammer to this." So we did that. We finally got something that had a DNA insert that was the right size.

The next step was to check the DNA sequence. The A sequence was all perfectly okay. The first one that Paco did, that was okay. We looked at this B-B one and every one that we got that was the right size had this funny little mistake in the sequence. So I looked at that and I thought about it overnight and I said, "Oh my god, they've messed up the synthesis of that chain." When making the oligonucleotides, Itakura's group were taking units of three, like G-T-C, and then hooking that up to T-T-G or T-G-A etc. The oligonuclotides were built in units of three. I looked at the DNA sequence data I was getting and said, "Somebody has flipped one of those units of three nucleotides around." Instead of joining G-C-A they must have accidentally used A-C-G. That's why this darn thing wouldn't come together right. By scaling up, we forced the thing to clone a chain that was not a good helix, and the bacteria must have fixed it up, but in the end gave the wrong sequence.

Hughes: How could that mistake have been made by the people doing the synthesis?

Kleid: Somebody took the triplet off the shelf and instead of reading G-C-A he read A-C-G (for example). I told Keiichi Itakura that we had found a mistake. I even told him which nucleotide to look in, because we could read the sequence that kept screwing up. The chain had to hybridize to itself and make a little helix, but it couldn't make a good one because the sequence was wrong. By forcing it, the bacterium said, "Well, somebody's making us do this." So it repaired the mistake that caused the sequence to be different. So that was the problem. Itakura's group made us a new oligonucleotide, and we finally got a clone of the B-B.

Research with and without City of Hope Scientists

Hughes: Was Itakura making the DNA for you?

Kleid: Right.

Hughes: And what was Riggs doing?

Kleid: Wondering why Dennis and Dave couldn't do this, I guess. [chuckles]

Hughes: You and Dave were working on your own?

Kleid: Kind of. Remember, our lab wasn't done. So we had to commute to LA to do this, because it was really difficult to figure out what the heck was going wrong. Our wives just wanted to see us again. So we brought the plasmids back to SRI, because I had all the DNA sequencing equipment there, and I was hiring these people. We couldn't work here at Genentech during those few weeks. So we worked during that month of May, when this problem was going on, at SRI. That's where we figured out the DNA sequence; the cloning steps were all done at City of Hope.

Hughes: What were you doing at City of Hope then? The cloning?

Kleid: Yes. There we did the cloning, and we picked the plasmids. I think we brought back plasmid DNA because sequencing was a lot of work in those days. That was a two- or three-day project, just to sequence. So we made all these plasmid preps and brought them back so we could see our wives again and we could do that step here. During May we finally found some that had the right size and the sequence mistake.

Hughes: Where was your lab when you were at City of Hope?

Kleid: It was in Art Riggs' lab. Art Riggs had about four or five labs and so he gave us a little corner. Well, it was actually almost a closet. It was literally the teeniest lab I'd ever seen in my life. I think there was just a hood and a tiny little bench.

Hughes: Did you interact with other people?

Kleid: The only ones that we worked with were Louise Shively and Rachelle Sailor, who were Art Riggs' technicians. Louise Shively worked with Art on the A-chain - B-chain reassociation experiment with authentic insulin.

To get back to the story: So we worked in Art's lab and finally got the problem figured out. We ordered a new piece of DNA, and then in June the Itakura group finished the synthesis of that one oligonucleotide that was wrong. Herb Heyneker came back from Holland to see how things were going.[1] Also he came here to look for a place to live, with the plan in the next month or two of bringing his wife and two little boys.

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[1]To backtrack a bit, when I committed to Bob that I wanted to join Genentech, I talked to Herb Heyneker on the phone, and we wrote letters back and forth. I said the same thing that I had said to Dave, "I'm not coming unless you're coming." So we had a little team there. Herb came to America on some kind of a scholarship from Holland which committed him to going back to the university in Leiden and working there. So he had to fulfill that commitment. I think in the end they were able to shorten it somehow.

In June the DNA was ready, so Dave and Herb [Heyneker] went down to Keiichi Itakura's lab, and they cloned with the good DNA to finally make the B-B part. That worked perfectly the first time. Now we were ready to start working here at Genentech itself. The lab was sufficiently equipped. Bob was very, very anxious for us to get out of SRI and come here.

The Kabi and Lilly Agreements

Hughes: Had Bob gone down with you to City of Hope?

Kleid: No. During that time he was dealing with the funding aspects of Genentech. He was negotiating with Kabi in Sweden and Eli Lilly. When I first met Swanson and Boyer this Lilly deal was all but closed, according to my understanding. Bob and Herb had hired an attorney, Tom Kiley, to help write an agreement. The agreement was going kind of slowly, but they had basically worked out what they wanted to agree to. Bob said, "Any day Lilly's going to sign it and we'll be okay." In the meantime they also talked to this Kabi company about doing the same thing with growth hormone. They were working on an agreement with Kabi which was similar to the one with Lilly. I was not told what the details of the agreements were. This was top secret. The secretary had it locked in a file cabinet. We were not going to be poking around in Bob's business deals.

Hughes: Was that all right with you?

Kleid: I didn't like it at all. [laughter]

Hughes: Why?

Kleid: Because I was used to being the boss. In my lab I knew exactly where the money was coming from. I always felt responsible for getting it. I didn't mind giving that responsibility up, but I thought I would be in the loop at least.

Sharon Carlock

Kleid: Sharon Carlock, the secretary, decided that <u>she</u> was in charge of Genentech. [chuckles]

Hughes: You mean rather than Bob?

Kleid: Rather than Bob? No, but in my mind she thought the one who was really in charge of Genentech was <u>Sharon</u>. She had the only typewriter. This was electric typewriter days. She sat right at the front door, and she answered all the phones. She helped get the insurance and paid the checks and all the millions of things you would have an administrative person do. In a company now I think there are probably three- or four-hundred people that have the jobs that she had.

One time I answered a phone call from one of the people going to bring in a dishwasher. They said that they were going to be able to deliver it next week. I said, "Okay, fine." Sharon said, "Next week! I told them to bring it tomorrow! Don't ever do that again! You messed up the whole thing!" So I really took so much of a dislike to her that I would come in the back door so I wouldn't have to look at her.

When they built the lab they decided to knock out a wall and put a window in so that our one little lab had one window into a hallway. She would come down that hallway and show people the facility. She would stand outside that window pointing at "her scientists." "There's my scientist. There's my other scientist." We were like little rats in a cage in this room with a window. I hated that.

Hughes: How did she and Bob get along?

Kleid: All right. She was very efficient. She typed <u>really</u> fast, although with a tremendous amount of typos. Eventually there was a rather serious falling out. She lasted exactly a year. I'm shocked that she lasted a whole year, but she did. We had a little party for her for being there a whole year. Dave Goeddel wrote a song, "Sharon the Mother of Genentech." He sang the song to her in the same tune as "Rudolph the Red-Nosed Reindeer." [singing] It had a double meaning--the <u>mother</u> of Genentech. [laughter] At some point she decided that Bob was not doing a good job, so she wrote a letter to one of the venture capital guys, [Thomas] Perkins, about what Bob should be doing. That was the end of her. [laughter]

Kleid-Goeddel Teamwork

Hughes: You said that much of your work at SRI was writing grants, etcetera. How was it having to get back to bench work?

Kleid: It was a lot better. I spent more than 80 percent of my time writing at SRI, and I couldn't do that very well. Now it was pure lab work. Dave was the one who learned how to do these things from John Little. So Dave and I worked together. I wasn't completely thumbs. A lot of experiments, you've got to do this step and this step, and Dave would take the lead on a lot of the steps. A lot of times we would do these backups. Just in case this didn't work we would make another plasmid prep or another thing like that. Dave would do three or four steps at the same time. I thought, "Just in case that one doesn't work, let's save the middle part and make sure we've got that step done." A lot of times we would go back to the backup, but sometimes we wouldn't.

Hughes: You were doing those backup experiments?

Kleid: We were working together. It took two people and a lot of steps, making the gels and doing the sequencing. I did most of the sequencing steps.

Hughes: Can you describe a typical day, if there was one?

Kleid: I can try. Let's say June 1978. Dave would drive over to my house in his little yellow Volkswagen. He would toot the horn at about six or so in the morning. I would leave my clothes right next to my bed. My wife was there of course and a little baby. We lived at that time in Menlo Park, right across from SRI. I would jump into my pants and throw my shirt on and then go outside and plop myself in the front seat and put the rest of my clothes on, and we would drive up. During the drive I would say, "Dave, what are we going to do today?" So we'd start getting focused on everything so that when we got there we wouldn't have to talk about it. "You're going to this; I'm going to this; we're going to do that."

Hughes: I read that he's a morning person and you're a night person.

Kleid: Right.

Hughes: But you were functioning pretty well after that rude awakening?

Kleid: I got another little nap on the way up. We got our coffee when we got there. I like to get up at the crack of 8:30. [laughter] He's up way earlier than that. We would drive home together and then somebody might have to come back. On the weekends, we would take turns. He might be there early, and I'd come in the afternoon.

Hughes: Were your families used to this routine?

Kleid: My wife was not that happy about it. Our wives got married to us when we were graduate students, so it was a continuation.

Hughes: They had never known anything else. [laughs]

Kleid: Right. We were absorbed and focused on what we were doing, and hopefully it would work so there would be food on the table.

Hughes: How did you feel about what to some people would be a real grind?

Kleid: That was <u>not</u> a problem. We thought about the experiments and what we had to do <u>all</u> the time, twenty-four hours a day, even when we were asleep, trying to think of what to do next. Like the problem with the sequence going wrong. That really drove us crazy for at least several weeks. You'd ask yourself, "Are we so bad at this, we can't get this stupid thing to work?" The first things scientists do when an experiment doesn't work is they blame themselves and their technique. So you just keep trying it again. You've got to take a step back and figure out what the heck's going on.

<u>Laboratory Assistants</u>

Hughes: Most days was it the two of you working away in this 30 ft. x 40 ft. room?

Kleid: We hired a couple of young people to help us, Frances Fields and Mark Backer. We hired them as technicians. I went to the Stanford job fair one day, I think it was in June, maybe May 1978. I put up my little sign, who I was, and those two came by. The only Stanford grads that wanted to interview Genentech were those two, so I hired them both pretty much on the spot. They came by Genentech and started working as soon as school was over.

Hughes: Did you have to train them?

Kleid: Complete training, yes.

Hughes: Were they biology majors?

Kleid: They were in science. What they needed to learn: How do you run the dishwasher? How do you make the bacterial culture plates? How do you pick bacterial colonies?

Hughes: They weren't doing any sequencing?

Kleid: No. We didn't have them do that. But they would help us make the gels and the reagents that went in the gels and the reagents that you grew the bacteria in.

Hughes: Did they work long hours as well?

Kleid: No. Fran Fields became a regular technician and a very good molecular biologist. She stayed at Genentech for at least ten years. Mark, after a year or two, went to work with Brian Sheehan on learning how to do the fermenters. He eventually went back to graduate school and is a very well-known young man these days. I remember when I introduced him to Bob Swanson and they talked to each other a little bit. Mark looked really young. Bob said, "You hired that space cadet?" [laughter] I told Dave what Bob had said, and Dave immediately gave Mark the nickname space cadet. Dave gave everybody nicknames.

Hughes: What was yours?

Kleid: I don't recall.

Recreation

Hughes: There are a lot of stories about the zany things that Genentech scientists did while they were waiting for experiments to mature.

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Kleid: In the early days we used to go fishing a lot. I may have mentioned that we fished off the point out here, Point San Bruno.

I was not a real fan of practical jokes, but Dave loved practical jokes. They could be as simple as putting a sign on somebody's back. I think that the diversion was something that he needed once in a while from being totally focused. A lot of really bright and very motivated people like to have fun too. I don't think people should get the impression that Genentech was filled with a bunch of jokers. We were very serious, but we played hard.

Hughes: You did everything hard.

More on the Insulin Project

Kleid: I want to get back to the insulin project. Once we got the plasmids made and hooked up with this beta-gal, we had to make our first little sample of insulin. As I told you, the yield was going to be incredibly small. We were able to hook these genes up to the end of beta-gal, grow it up in bacteria, and then clip off the two insulin chains. Then Dave took the samples down to City of Hope and with Art Riggs reassembled the A- and B-chains. That's the data that you see in Table 2 of our paper.[1] There was enough insulin activity that you could see it with a radioimmunoassay. Based on that we announced that we had made insulin. This paper was received in October 1978. During August and September we were able to make this little sample.

More on the Agreements with Kabi and Lilly

Kleid: All spring and summer Swanson was still negotiating with Eli Lilly to get them to agree to work with us. It came down to where Bob said, "Look, I don't think that Lilly is going to agree to sign this agreement until we make some insulin. So what I'd like to do is tell them to fish or cut bait on that day. We're going to make this sample. Then we're going to tell Lilly that we're going to announce it, and either you are in or you're not." So that seemed to have done the trick.

In the meantime Genentech also signed an agreement with Kabi, I think in August. So in August the Kabi agreement was signed; in September the insulin was signed.

Hughes: Who was working on growth hormone?

Kleid: Nobody at that point. They were just working on the deal for it.

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[1]D.V. Goeddel, D.G. Kleid, F. Bolivar, H.L. Heyneker, D.G. Yansura, R. Crea, T. Hirose, R. Kraszewski, K. Itakura, and A.D. Riggs. Expression in *E. coli* of chemically synthesized genes for human insulin. *Proc. Natl. Acad. Sci. USA* 76, 106-110 (1979).

Hughes: Why would Kabi sign a deal when there wasn't even a microorganism with a growth hormone gene in it?

Kleid: As I said, I learned all about this after the fact. Both the Lilly and the Kabi agreements were set up with benchmarks. The idea was that the two companies would fund the research to get it done. Of course, people part with their research funds very gingerly. So Swanson said, "Look, you don't have to pay anything until we make this particular goal, and if we make that goal, you cut us a check." Then he jerry-rigged another goal, that if we did the next benchmark, then we would get another chunk and go on like that. So we would get paid by making the goals rather than Lilly and Kabi having to pay salaries and for endless research. So that's how we convinced Lilly and Kabi to sign up.

Kabi was interested in growth hormone. They already made growth hormone from cadaver pituitaries, and they were interested in this new technology. Herb and Bob had gone to Sweden to visit Kabi, and they were very interested. So they were a lot quicker to sign the agreement Lilly was. The business people at Lilly really dragged it out and really nailed down each of these steps, and they kept getting more and more onerous. Finally we made the little sample, and Bob said, "We're going to announce our success at a press conference." Art was kind of nervous about that so Bob said, "Art, you go give a talk somewhere. You present the work and then on the same day or the next day we will do this press release."

Hughes: Why was Riggs uncomfortable with a press conference?

Kleid: I don't think he was uncomfortable with that, but he was uncomfortable with announcing a scientific result first in a press conference; he would rather first have some kind of scientific announcement. The ideal thing would be to publish it first and then have the press conference. The publication came out in January of '79, so that would be six months after doing it. By that time everybody in the world would have found out about it. So why don't we do this: have a little seminar and announce it there. I think Riggs went to Caltech and gave a little seminar. Then we did this press release which was organized by the City of Hope at the City of Hope.

Yet More on the Insulin Project

Trying to Increase Insulin Yield

Hughes: I'm hoping that you'll talk about that in some detail, but first let me ask you more about the science. What were you worrying about most?

Kleid: I was worried about the yields: Could you make a sample of a drug from these bacteria using this process? The beta-gal with the little chain on the end was about three to four percent of the total bacteria's protein, which seemed to be a lot. That was shown in Figure 2 of our paper. If you lyse the bacteria and put them on a gel, you can see all the different proteins of the bacteria. The very dominant one is beta-gal with the A- or B-chain on it. This represented the whole bacteria. If we lyse the bacteria, spin them down, and then in the pellet was the fusion protein.

We could see that there was a lot of it in there (now about 30-50% of the protein in the sample), but it still was very low yield when all the steps that are still needed are considered.

There was a similar situation in the somatostatin purification. It looked like almost 5% of the total protein in the bacteria was the beta-gal somatostatin fusion protein. Normally the beta-gal is a soluble enzyme present in less than about 0.1%. You imagine this soluble enzyme inside a bacterium doing its thing. And then you wonder, "How can a bacterium live with all of this enzyme in there? How is it going to function?" I was pretending that I was inside of a bacterium dealing with all of these foreign molecules. "We can't do this."

Dr. Riggs had found that when he broke the bacterium up, the beta-gal as a somatostatin fusion protein was precipitated. So I said to myself, "It's <u>not</u> dissolved. That's what's happening: this protein is not soluble anymore; it's not folded up properly like the real beta-gal." So I bought a microscope. I said, "I bet we can see that stuff." I actually did that experiment. I've got a photo that I took through the microscope in my notebook. This is exciting. This phenomenon is one of the reasons why Genentech exists today. The bacteria would take up this unfolded material, and as they were swimming around, or spinning around, they were acting like little centrifuges, and they would precipitate out the protein so you could actually see it in the bacteria as little tiny balls. I brought my camera to work and took pictures.

Hughes: This was with a light microscope?

Kleid: It was with a phase-contrast light microscope. All I did was put my camera right on top and take a picture right through the microscope using my regular 35 mm camera. [Reaches for photographs] Years later, during some litigation issues that followed, I blew up some of these pictures. Maybe one of these you might want to put in the oral history. We're looking at a cover slip and a little drop of broth. The bacteria are in there and they're swimming around. The magnification is up pretty high, and it's phase contrast so you can see the bacteria. Do you see these little bacteria here?

Hughes: Yes.

Kleid: Those are *E. coli*. The grid here is used by a microbiologist to tell what the density of your culture is because you can count how many are in this square, and you can figure out how dense your culture is. If you look closely at these bacteria, you see that they have a little bright spot right at the end.

Hughes: Oh, yes, I see.

Kleid: So I showed these to everybody, including Herb Boyer, and I said, "Look at those little bright spots. That is this precipitated protein. When you break open the bacteria the bright spots of protein precipitate. That's why the *E. coli* can survive with all this material in there.

Hughes: This finding must have resonated in terms of how Genentech might eventually collect recombinant proteins.

Kleid: Exactly. In fact, it was one of the major differences between us and Wally Gilbert. Gilbert's idea was to get the bacteria to secrete the insulin out into the media and then have a continuous

culture and just suck the media off. After looking at this, our idea was completely different: You take the bacteria, and you spin them down, and then you break them open, and dissolve them into some kind of medium. Then you spin them down again and collect these refractile bodies. You can purify out pretty well in one step; you're 90 percent of the way to pure fusion protein with just one step.

Hughes: And that's what you did.

Kleid: That's what we did. That was the basis of our process.

After this announcement that we'd done it [cloned and expressed the human insulin gene], the next step was to go talk to Lilly and say, "We've got a process that actually has some possibilities here."

Hughes: Was Lilly persuaded even though you had expressed so little insulin?

Kleid: No. They were <u>not</u> persuaded, and that was the next thing. In August the Kabi agreement was signed for human growth hormone work. Now that it was signed Bob started sharing with us a little bit about what he had agreed to. This Kabi agreement had benchmarks. The first benchmark was to decide, how are we going to do growth hormone? Are we going to do it with a cDNA, or are we going to do it synthetically? The agreement said, "The first thing we're going to do is to choose which way to go." I remember talking to Dave about it after hearing about this benchmark. "Look, we can do a gene that's part synthetic and part cDNA so that we can hook it up with a start codon right in the front and no fusion protein. Maybe the bacteria won't chew up the protein product. In the somatostatin experiment, the bacteria chewed it up. In those early days we thought the bacteria were going to chew everything up that was small. But that wasn't reason. Now we know they don't chew it up because they're precipitating it. So the proteases can't eat the protein up when its not soluble.

Hughes: Did the bacteria actually sequester the foreign protein?

Kleid: In these little balls.

Hughes: So the protein's isolated from the cytoplasm and nonfunctional as far as the bacterium is concerned?

Kleid: It's precipitated out so that the proteases, which are soluble proteins, don't see it, and the protein is protected that way. It's kind of like, believe it or not, the feces of bacteria. They constantly make proteins that get denatured, and they spin them down in these little particles, and it doesn't bother them anymore. But we didn't know anything about it in the 1970s. Nobody at the time had ever described how bacteria deal with denatured proteins. They don't chop them up to bits; a lot of times they just precipitate them.

Hughes: Which was fortunate for Genentech, wasn't it?

Kleid: It was incredibly fortunate. When you listen to Swanson tell the story about somatostatin, it was that they made somatostatin, and then they assayed for it, and it was <u>gone</u>. He was <u>unbelievably</u> upset. So Riggs said, "Let's make the molecule bigger." So they made it bigger and it worked.

And everybody was talking about, "Let's just make it bigger." But I thought about this: Making it bigger is not going to do it because you would expect such proteins to have a lots and lots of places for the protease to chew and you would have a whole smear. To me just making it bigger would be worse because you would not see the kind of band on the gel that was seen. I got this microscope and was able to say, "It's not bigger in molecular size [that's the issue], it's solubility. The protein is not folded up right, and it's coming out of solution. So that led to growth hormone, saying, "We don't really need to hook it up to beta-gal and make it bigger, all we need to do is to make it so that it will precipitate into insoluble balls." So the question is, Why is it doing this?

Protein Folding

Hughes: Was it a given in those days that proteins to function had to be folded correctly?

Kleid: Oh, yes.

Hughes: Was Genentech worried: Okay, we can produce this protein, but is it going to fold right?

Kleid: Exactly. When you're dealing with tiny proteins like somatostatin, there's only one fold. It folds kind of in half and makes a disulfide bond. In insulin, Art with the Katsoyannis experiment was able to take insulin apart and reassemble it. Growth hormone, what would happen when you did that? Would you be able to get the three-dimensional structure back?

It turned out that there was work at UCSF by C.H. Li where they had chemically synthesized insulin and growth hormone. He had done some work with breaking growth hormone apart and reassembling it. You can count on one hand the proteins you're able to denature and refold--that would be critical. You're absolutely right. You're not going to be able to make anything useful unless you're able to fold it up.

Hughes: Do you think that Swanson, when he started out on this venture, realized all the scientific hangups that there could be?

Kleid: No. He had no clue.

Hughes: What about Herb Boyer?

Kleid: My opinion was that he was kind of ambivalent: If you guys can work it out, wow, he'd have a company. If we couldn't, "No skin off my nose; at least we gave it a good try."

Hughes: Did you ever talk to Herb about the problem of protein folding?

Kleid: We did. In fact, he was the one who named these things refractal bodies because they were refracting light and glowing. He was there to talk about this stuff. Then when we talked about that semi-synthetic gene idea for growth hormone, he was there; we could bounce that off him.

The problems with this process were that the yield was so astoundingly low that we still weren't close to being able to commercialize anything.

Biological Functionality of Recombinant Insulin

Hughes: When production of human insulin was announced at the press conference, did you know that it was functional?

Kleid: The radioimmunoassay [RIA] was to see if the three-dimensional structure was there. All hormones need to do is to bind to their receptor. Insulin binds to its receptor and then the receptor turns on. The goal with the hormone is kind of lucky because you just want it to bind to the receptor and turn on the cell.

Hughes: And so you were pretty sure that your insulin would work.

Kleid: Right. If you were making an enzyme, on the other hand, then your assay would be to see if it's chewing things up properly. But with a hormone we were pretty confident, although there was quite a bit of criticism that we didn't do a biological assay on insulin. We just showed that we had an RIA-active sample.

Hughes: Did it occur to you to do a biological assay?

Kleid: Well, I'm a chemist. From an organic chemist's point of view, you say you've got the three-dimensional structure, "What's the problem? You want to do biology? That's a biologist's job."

Hughes: Was Dave thinking the same way?

Kleid: Right. We were both of the same mind set: We've got the RIA data. Our goal was to make a tiny bit of this stuff and show that we were actually folding it up and it was binding to the insulin antibody. The insulin antibody is not that much different than the insulin receptor. Unless something very strange is happening, the insulin should be okay; it should be the right thing. We know, amino acid by amino acid, we've got them right. We know that they oxidize right; it binds to the antibody. That's it! We demonstrated this proof of structure rather than [proof of] activity. It was not a mouse, after all; it was just a physical protein.

The Press Conference, September 6, 1978

Hughes: Now, let's talk about the press conference.

Kleid: The famous press conference.

Hughes: Why was it held at City of Hope?

Kleid: City of Hope was the main player because Keiichi Itakura made the DNA, and we did a lot of the cloning down there. Physically, all Genentech was was a warehouse. City of Hope had a scientific group that did this kind of thing, and a PR department. City of Hope raises a lot of money, that's one of the major things they do, and so this press conference would be good for them. They could have a press conference to show that they're really making progress. It would help them raise money. Who cares about going to Genentech? So City of Hope organized it.

You probably read the Stephen Hall account of the conference.[1] It still seems like it was yesterday. We went down and this auditorium was just filled with people with cameras. It might have been thirty or forty people with cameras and lights and stuff. They told us to come up and sit on the stage. We had a row of chairs, the City of Hope people on one side, Genentech on the other. A City of Hope scientist, Dr. Rachmiel Levine, who had worked on insulin for many years, started taking questions. They were asking him how all this was done. He explained all of these technical things but was getting it half wrong because he didn't know anything. He didn't bother to introduce us; he just started talking. Dave was sitting next to me and he was getting mad about this. "Who is this guy? That's not right!" The question came up about the dangers. Is this technology dangerous and is this ethical to do? It was already an issue about playing with mother nature's genetic code. "God wrote that code. What are you guys doing with it?" (That's my thinking, not what anybody said.)

So here comes this ethics and safety question. Dave said, "Get up there, get up there." So I went up there to try to get Levine to let somebody else talk. I don't know why, but I end up doing it. I started answering the question for Levine. My answer was kind of funny. The questioner had said, "Genentech made this insulin and isn't that dangerous?" I said, "Well, if you say we made insulin in these bacteria then that's a lie. We didn't really make insulin; we made these fusion proteins, and then cut off the A-chain and then the B-chain and reassembled them. So there's no safety issue here as far as bacteria making insulin." But my first sentence was, "If you say we made insulin, that would be a lie." That was <u>really</u> funny. [chuckles]

Then the next question came up and somebody else, Art Riggs I think, came up. Finally they decided, "Well, let's introduce everybody." So they introduced us all. Then they said, "Bob, why don't you have a few things to say." So Bob Swanson stood up there at the microphone and then all the lights went out. They had used so many lights in this building, they tripped the circuit breaker and all the lights went out. I don't think Bob got a chance to say anything. So that was the end of the press conference.

Some of the reporters wanted to talk one on one. Connie Chung used to work for a TV station in LA. She came back to the lab with us and wanted to see all these things. She brought her camera crew and a microphone and interviewed me. We went over to the refrigerator where we kept all the plasmid preps. They were in little tiny vials about an inch high. I wanted to show her one of those vials and opened the refrigerator a little too hard. The rack came flying out and all these little vials went flying all over the floor. [laughing] So I said, "Maybe we should clean that up and try this again."

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[1]Stephen Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene*, Redmond, WA: Tempus Books, 1987. [SSH]

Hughes: This was being videotaped?

Kleid: Yes, with Connie Chung right there. Luckily there wasn't anything radioactive in there.

We had flown down to LA and we flew back the same day. By the time we landed at San Francisco airport the evening paper had came out and there we were. Our story was right on the front page.

Eli Lilly had signed the agreement the day before so it could be announced at the press conference on September 5 that they were going to support this project. We made a prediction that we were going to be selling insulin in five years. In fact, Connie Chung asked, "How long is it going to take?" I said, "Oh, I bet you we can do it in five years." I had certainly caught the Bob Swanson spirit.

Collaborating with Lilly

Kleid: The next thing we did was to introduce this project to Eli Lilly because their scientists now wanted to hear about it. So we went to Indianapolis, and we had a meeting with all their scientists. It was huge--twenty people on each side of the table. We explained to them our experiment. Then they said, "How much insulin can you make in these bacteria?" They did a little back-of-the-envelope calculation based on what we said. "You're going to have to get the yield up about fifty times--fifty times--in order even to be close to the production levels that are required." Then they gave us a tour of the plant where they made insulin. Giant train cars came with frozen pancreatic glands which they pumped through this giant machine which ground them up and extracted insulin, and then did all these different steps and out came crystallized bovine and pork insulin.

The insulin they sold diabetics came in a little bottle that cost about seven dollars. They figured if they did human insulin by this recombinant technique maybe they could raise the price to ten or eleven, but if they went any higher the diabetics would scream bloody murder because it would be too expensive for them. The real killer was that Lilly did not want to lose its profit margin. The cost of goods to sales was a good chunk of change. I think it was in the range of 80 percent. It cost Lilly 20 percent of that seven dollars to make that vial and fill it up with insulin. What they were interested in was keeping the profit margin at about the same. So Genentech's manufacturing costs had to be down in that same two-dollar range or else they weren't going to do it.[1] Why would they sell something if they made less money than on the existing product? It made no sense to them to spend all of this money on this project if in the end they would be making less money.

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[1]They figured we were at about $100 per vial--about 50 times too much.

The Agreement with Lilly

Hughes: This was a different way of doing science than you'd ever done before, right? The commercial aspect was definitely shaping Genentech procedure.

Kleid: That's for sure.

Hughes: How did you feel about that?

Kleid: I was comfortable with it until Bob shared with us this agreement that he had made with Lilly. Remember I was telling you about the benchmarks? That if we reached a certain benchmark we got a certain check? Well, we got the first check which was when we made a sample. I don't remember all of them, but the next benchmark was to make a sample that was five micrograms so that they could study it to make sure it was okay, to make sure *E. coli* wasn't doing something weird to the amino acid sequence. The next benchmark was a yield thing. Another one was another yield thing. This second yield benchmark was impossible!

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Kleid: In order to meet this benchmark, half the bacteria would have to contain this fusion protein with the A-chain and the B-chain. That was impossible! Then another nice [meant facetiously] thing in the agreement was there were dates. If we didn't make these benchmarks by a certain date written in the agreement, then Eli Lilly could take where we were at that stage, go off with the bacteria, and not owe us a dime.

Hughes: Who set these benchmarks?

Kleid: Herb Boyer and Bob and Lilly! I thought they were naive. They had a very rosy outlook about what was going to happen. When I first looked at these benchmark agreements in 1979, they were not talking about rosy outlook, they were talking about my future. They had signed something that said these people were going to be able to walk off with this bug if we couldn't make a certain amount of insulin by a certain date that was fifty times away from where we were. Fifty times away! And that was even when five percent of the cell was this one fusion protein. I was very upset. I said, "This is impossible."

Hughes: How did you handle the situation?

Kleid: Bob said, "Dennis, this is possible, what are you talking about? It's not impossible. I don't want to hear that word, 'impossible.' Just tell me what you need to accomplish it." (There's some real sympathy for you.)

What were we going to do now? The only one that could possibly help us out was God. Nobody had ever made a protein in a bacterium with that kind of yield. This particular phenomenon had not been experienced on earth with I don't know how many years of bacterial evolution. Yet Bob says, "What are you talking about, 'impossible'? I don't like hearing that word."

Hughes: How did you meet the benchmark, or did you?

Kleid: Well, we went back to square one. Yes, we did meet the benchmark, and that insulin was on sale five years later.

Hughes: With that 50 times higher percentage in the cell?

Kleid: Yes. Those bacteria did it! We tried to figure out how to increase the yield. We knew that this beta-gal, 1006 amino acids with a little chunk on the end, was not going to ever make it. But if the problem was solubility-- One idea I had was let's hook the A-chain and B-chain together and make a polymer of A- and B-chains so that this fusion protein was just pure A-chain B-chain. I worked on that and made these polymers of A-chain and B-chain.

The other problem was associated with the promoter. The promoter causes the messenger RNA to get made and then the messenger RNA gets read and turned into protein. We thought maybe we could get better *E. coli* promoters to direct higher levels of message, so Herb Heyneker and I worked on that. That was our project. Dave went and worked on growth hormone. Once the insulin paper was out, he never worked on insulin again.

Hughes: Because he was more interested in growth hormone?

Kleid: Interferon was the one that he wanted to do. Growth hormone was going to be Seeburg's project.

Dave was with us on that trip, looking at the Indianapolis setup Lilly had for making insulin. The chances of us replacing that plant with our process I thought was going to be a longshot. Let's try to make something other than insulin that is really valuable, I think was Dave's first thought. Interferon in the microgram range was selling for $100,000. The value per milligram of growth hormone was also way up there. So those had a chance of becoming commercial viable products.

Hughes: But you stuck with the insulin a bit longer.

Kleid: I stuck with it for the next couple, three years.

Hughes: Tell me what you were doing in those years.

Improving Techniques to Produce Higher Yields

Kleid: The first thing was trying to figure out a better promoter, and we tried three or four or five different promoters. Then we tried seeing how the ribosome binding site might influence things.

Then Giuseppe Miozzari joined our company along with several other people. He had come from Dr. Charles Yanofsky's lab at Stanford, and he had studied a particular promoter system called the tryp promoter, for the amino acid tryptophan. It turns out that bacteria are very

sensitive to needs for tryptophan. They can make a ton of this amino acid tryptophan or they can make none. The bacteria have several levels of control. There's an off switch and then there's a dimmer, and then there's another off switch and another dimmer. They can make tiny amounts but then if they need some right away they can just turn it all on and blast. We got rid of all those switches except for one, the trp repressor and operator, so that we had some control over it.

Giuseppe and Herb did this experiment with this tryptophan promoter. I remember, Herb had to go back to Holland at Christmas of 1979. He set up this experiment, gave it to my technician, Barbara Small, and went off to Holland. Then we ran this gel, and we saw these bands like you see here in figure 2 of our 1979 insulin paper. Those are about 5% of the total protein in the cell. But with this new tryptophan system, when you looked at the whole bacterium, the fusion protein was ten times more than that without even breaking the cells open. So the cells were making half of their cell weight in this one fusion protein. It was amazing. You could grow the bacteria up in regular media and then you'd dilute them to media that didn't have any tryptophan. Then all they did was make that protein. They would not be able to live turning out that much protein. But if you kept the promoter off and grew up the bacteria in the presence of tryptophan, and then dumped the cells into media that didn't have it, that promoter turned on and they virtually stopped replicating and just made our product..

Hughes: You'd think the bacteria would die in the process.

Kleid: They were literally dying in the process and choking themselves and filling up with this stuff. We saw that result and we said, "Oh my god, we've got it. It's going to work." So we switched from the beta-gal to this tryptophan system and put in the A-chain and the B-chain with a 200 amino acid fusion protein (instead of 1000) that was made in yields ten times as much. We had our fifty times higher.

By that time we had made proinsulin and hooked that to this same fusion protein in the same system. In all the other experiments I had done and sent to Lilly, I never got any feedback. But this one we decided, "All right, we're going to give it to them. They're going to figure this out, and we're going to work on it here too." By that time we had some protein chemists, and we went ahead and helped to develop a process to use that system to make human insulin

Lilly Develops a Commercial Process for Insulin

Kleid: In the meantime, Lilly did go forward with the beta-gal and scaled that up. Even though the yield was so incredibly small, they made enough to do clinical trials with it during 1980-83. They were committed to doing it. It was not economic. They were not happy; they were miserable. Somebody at Lilly said, "You're going to figure out how to do this." They went ahead with the beta-gal until we gave them the tryp. And then they switched to the tryp, and they were extremely happy. Then they were able to grow these bacteria and fill them with 60, 70 percent of this one thing. In fact, they eventually were so excited about it they made a publication showing the bacteria filled with this tryptophan fusion protein together with the proinsulin. So they were able to turn that into a commercial process. They were able to make

the stuff and maintain their profit margin and start selling human insulin. It was absolutely incredible.

Hughes: Talk about the scientific interaction with Lilly. How much interaction was there to make this project a commercial venture?

Kleid: In the beginning there were formal meetings. We decided that we were going to share written reports and visit Lilly, instead of calling up. We started some informal communication early on, and there was just absolutely no response. So when we did the formal meetings it seemed to work out better. Mike Ross was one of our leaders on this and Ron Wetzel. These guys were a little more organized than me. They could get these things all nicely written up, and they had a fairly good interaction with the Lilly people.

Hughes: Does that suggest that big pharma was used to working according to protocol, not with an entrepreneurial start-up?

Kleid: They had a different way of working. They had report after report after report. The notebooks would be scrupulously written and countersigned at the bottom for patent reasons. They had meetings constantly to go over these reports. It was incredibly structured.

At Genentech absolutely everything was oral. We had our Friday ho-hos. We were lucky if people wrote in their notebooks. It says right in the front of the notebook what to do and why to do it. "Write in your notebook, have it countersigned, keep it in ink. If there's any cross-outs be sure and initial them." Nobody seemed to know that this page was there. [laughter] Bob would thumb through these once in a while and say,"Where are the signatures?"

At Eli Lilly-- I can't share with you because eventually we did a litigation with Lilly, and I was privy to all of their documents from this time. There's a protective order that says that I'm not allowed to share with you. A lot of it is published by the judge however. The judge eventually made decisions, and so I can tell you about that. In general, the way Lilly and Genentech worked was <u>absolutely</u> different. But I have to say, Lilly did a good job. They had a project ahead of them that was viewed by the insiders as impossible, and then all of sudden it wasn't impossible; it was possible.

Lilly's Agreement with UC

Kleid: The switch had an impact on Goodman's group. It turned out that UC was also working with Eli Lilly on insulin. Genentech had no contact with the UC group at all. The Lilly people would come to visit Genentech, and then we thought they were going home but instead they were going over to visit UC.

Hughes: And you didn't know that?

Kleid: No. UC had an agreement with Lilly that if they were successful in expressing human insulin they would be able to negotiate a royalty rate on the sales of insulin. We had one where it was

already written what the royalty rate was. Lilly would much rather have UC end up being successful and then just dump Genentech because we couldn't make one of these benchmarks, like the yield benchmark. Lilly was absolutely positive we were never going to be able to make that benchmark. They worked with UC so they wouldn't be at risk to have to pay this royalty.

Hughes: Do you know which contract was signed first?

Kleid: The UC one was way earlier. It wasn't as specific. It didn't have any benchmarks. It had very little money associated with it, just little research funds.

Hughes: I don't know that academia worked to benchmarks in that era.

Kleid: Nobody did. This is the first time I had ever heard of it. One of the things they credit Swanson for in this industry is it did become a pattern with small companies to sell benchmarks rather than sell time. It's a rather different concept. Although we never did one with the time on it again. That was the first and only agreement where the benchmarks had a time to meet the benchmark or your out. I was furious at that, because it was just too much of a risk.

Swanson grew to like the idea of having no times. In the early years of Genentech where we would hit the benchmark before the end of a quarter so that we could put the money on our books. The investment community wanted to see if we were profitable or not, so we would meet these benchmarks by the end of a quarter. We were internally motivated instead of having a guillotine hanging over us, that if we didn't make it in time the other company gets to walk off with all our stuff. That was nuts!

Genentech's Early Management Team

Hughes: Bob came around to understanding why it was a good idea not to have dated benchmarks?

Kleid: Right. That's when there was a gradual switch in 1979-80; the scientists decided, "We need to be part of management. We are not going to have this arrangement where Bob signs the agreements and never tells us about them. We're going to be part of the whole process."

Hughes: When did that happen?

Kleid: That started in 1979. We didn't go on strike [chuckles], but we decided that we would have a scientist on management. We decided to take turns being in charge. The first quarter was Herb Heyneker. He was our token VP for a quarter in 1979.

Hughes: And that meant that he went to all executive meetings?

Kleid: Yes. The executive committee was a committee of four or five. It was tiny but it was already doing important things. There was Swanson and Brian Sheehan and Fred Middleton who was Bob's old buddy from MIT. (They belonged to the same fraternity.) Then we got Bob Byrnes who was VP of Marketing. [chuckles]

Hughes: Were these new positions for show?

Kleid: No, Bob was convinced we needed them and the earlier the better. It made no sense to spend all this time and energy researching something and making a product that there was no market for. We were negotiating with others all this time, so now we needed the marketing guy to take over. We were going to do this deal with Hoffmann-La Roche and deals with some Japanese companies. So marketing was the marketing of "our technology" at this early stage of Genentech.

Hughes: Not so much marketing a product.

Kleid: Right, marketing a technology. Then Tom Kiley came to join us. Now you had quite a little crew there. Herb Heyneker was the first token VP of the research group. Giuseppe Miozzari was the next, for the next quarter. It turned out that he had more talent in this area. He was not like Heyneker, although Heyneker is a very excellent businessman. He's made dozens of companies. Miozzari was from Switzerland and was a very good-looking guy and very organized, and he was perfect for this job. The business guys felt perfect rapport with him. He was able to communicate to us what we needed. He brought the tryp promoter. So he was a good scientist, but he didn't like working in the lab that much. So he was happy doing this management thing.

We then developed a little structure so that instead of everybody working for Bob, now we had a little management group. Giuseppe was in charge. So we set up a molecular biology group, and six of us would report to Giuseppe. Eventually we decided, "Let's divide that up a little more. We can have a molecular biology and a protein group." Bob Byrnes helped us turn the swampy-type organization into one that actually had a little structure where you could go to somebody and they could actually figure out what was going on. Although it was still all oral; there were still not a lot of written reports. But we had communication.

The Complementary DNA Approach to Insulin

Hughes: Let's go back for a minute to what was happening at UCSF. Tell me about the complementary DNA route as a means for producing insulin.

Kleid: It had one practical problem right at the beginning, which was how do you hook up your *E. coli* gene to your cDNA? How do you make the marriage so that the *E. coli* thinks it's making, for example, the enzyme for tryptophan, when it's really making insulin? The insulin gene had a signal sequence that was recognized by cells to cause the protein to get secreted and then folded and then part of this insulin chain--the C-chain gets removed. Mammalian cells can carry out all those processes, but *E. coli* couldn't. So you have your cDNA, what do you have then? You've still got exactly the same problem we had, which was yield. But we had synthetic genes that we could pop out and keep trying different promoters. We set it up so that the little chain could be hooked up to different kinds of promoters to try to figure out which one would work the best or which fusion protein was the best to make the yield. Whereas they just had a string of cDNA; it was a dead end.

The UC-Lilly-Genentech Litigations, 1986-1999

Kleid: We eventually gave to Lilly this pro-insulin hooked to the tryp. They originally made insulin with the A-chain and the B-chain in two separate bugs. Then after three or four years Lilly switched over to the pro-insulin, so they made the two chains linked together with the insulin C-chain in one bug, and then did the folding and the clipping out of the C-chain. That's a lot more steps. It took them quite a while to develop that protocol and it was a very major project. I think in the end the economics of going there was probably break even because they had to add enzymes and then do another purification step. So I don't know why Lilly spent a lot of time doing that. That was more what UC was thinking: to use the cDNA in this pro-insulin type project. Now our Genentech DNA had synthetic DNA in the front and then it was cDNA in the back, so that you could hook it up just right, to for example, the tryptophan promoter fusion protein.

That pro-insulin process using the tryptophan fusion was developed by Lilly, and then UC said, "That's covered by our patent. You're infringing our patent." UC wanted to get their royalties from Lilly for using Genentech's semi-synthetic cDNA.

Hughes: That was a recent case?

Kleid: Well, that was started in 1990 and finally ended with UC on the losing side in 1997.[1] But the litigation actually started earlier with Lilly wanting to make growth hormone, and they worked with UC on growth hormone. We (Genentech), had the patents on making growth hormone. So Lilly sued us in Indianapolis to knock out our patents.[2] They also sued us in England and in France and in Germany, all over the world, to knock out our growth hormone patents so they could do growth hormone. So we were in this big battle. Then, when we got their documents--and this is in some of the judges' decisions--we alleged that they used our insulin plasmids with the tryp promoter in the Lilly- UC growth hormone project.[3] These cases were later all joined together in a "Multi-District Litigation" in Indianapolis.[4]

Our agreement with Lilly was written so that Lilly could use our bacteria to make human insulin and be free from patent litigation.[5] In fact, these very tryptophan-fusion protein-making bugs with the A-chain, B-chain, and pro-insulin, I gave to Lilly myself--made with my own hands. For twenty years Lilly used those. Lilly had taken those plasmids, cut out the insulin

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[1]Regents of the Univ. of Cal. *v.* Eli Lilly & Co. 90-0373-DLJ (N.D. Ca); Regents of the Univ. of Cal. *v.* Eli Lilly & Co., 119 F.3d 1559; 43 USPQ2d 1398 (Fed. Cir. 1997).

[2]Eli Lilly & Co. *v.* Genentech, Inc. IP-87-0219-C (S.D. Ind.).

[3]Genentech, Inc. *v.* Eli Lilly & Co. IP-88-1463-C (S.D. Ind.), Genentech, Inc. *v.* Eli Lilly & Co. & Regents of the Univ. of Cal. IP-90-1679-C-D/G (S.D. Ind.).

[4]MDL Docket No. MDL 912.

[5]When the agreements were written there a cloud over patent applications then pending that were directed to living matter [see *Diamond v. Chakrabarty*].

DNA, and put in growth hormone DNA. That was a no-no according to our agreement. So we countersued Lilly for violating that agreement and for infringing one of our patents. Lilly's defense was that they didn't know that the agreement said they weren't supposed to use them. Their other defense was that I told them it was okay, which was very maddening. I didn't tell them anything like that. The agreement said, "You will use these bugs for insulin, and when you're done, you'll give them back to Genentech." The agreement was kind of like a loan: You can use these bugs to make insulin, and when you don't want to use them anymore you give them back.

Hughes: My understanding is that one of the premises under which Genentech operated from the very early days was to keep the technology, not to sell it.

Kleid: To sell the rights to it and not the technology itself. Bob and Tom Kiley figured that the technology after twenty years would probably be superceded by new technology. But during the first twenty years or so you could use our bugs to make human insulin, and we would get royalties on your using our bugs. But don't play with them. It was kind of naive, but at any rate, that's what the concept was. We'll give them our magic bugs.

Hughes: But what else could Genentech have done?

Kleid: Well, you're right, there weren't many other choices. The other was to patent the technology, which we did, but at that time we didn't know if we were going to get patents on this technology. There was a case pending at that time, *Diamond v. Chakrabarty*, about patenting life forms that went all the way to the Supreme Court. The [U.S.] Patent Office could flush all the patents that had anything to do with life forms, and ours along with it. We were making these physical genes and using them in organisms. So it seemed to us that the processes for making those genes and patents on the chemicals themselves was patentable. The situation was a little bit tricky, but with the fusion proteins and the semi-synthetic genes, these were unique little gadgets. Our patent attorney, Tom Kiley, thought we could definitely patent those little technology pieces. But then an infringer could change a little thing here and there, so we needed to claim these unique little gadgets broadly. We didn't know how that was going to turn out.

In the end, the way Bob and Tom decided to handle that was, we will give you, the licensee, the bugs for this particular use, and if you don't want to use them anymore, give them back and the contract's over. That was also an issue in one of these cases because Lilly claimed that was patent misuse. The bugs are patented and you are tying the patent license to our use of these bug for making insulin. So they said technically it's an illegal tying arrangement. Of course there were no patents when we wrote the agreements.

That case lasted eight years, and eventually Lilly settled the Genentech vs Lilly and Lilly vs Genentech growth hormone cases. They wrote us a nice big check for $145 million for settling those cases. What they paid the money for is not really important. They never agreed that they infringed any of our patents or violated any agreements, so that should be clear. At the end of the day with this settlement Lilly did not say, "We plead guilty." When it started, Lilly wanted to get into growth hormone, and the only way to do that was to knock out our patents. Genentech brought this countersuit.

All together twelve Genentech patents and this dispute were in this case. Then Lilly decided, "We need some more ammunition. We're just the defense here." So they convinced UC to sue Genentech under UC's growth hormone patent. That is the case that went all the way back to Peter Seeburg.

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Kleid: Lilly told UC, "We're going to consider taking a license under your insulin patents and we will take a license under your growth hormone patent only if you sue Genentech under that growth hormone patent." So UC signed up on the growth hormone deal. They arranged an agreement, they got royalties for Lilly's growth hormone. Then UC sued Genentech under the growth hormone patent. On the insulin side, Lilly stiffed them. The growth hormone involved small royalties, but the insulin was going to be a big number. Lilly stiffed UC, so UC ended up suing Lilly. Now we had a three-way litigation: Lilly sued Genentech; Genentech sued Lilly back; Lilly convinced UC to sue Genentech; then UC sued Lilly. This involved all kinds of cases all over the place--in Indianapolis and in California. They ended up over the years getting all balled up into one giant case (see the footnotes above). It went into multi-district litigation. They put a multi-district litigation judge in charge, the Indianapolis judge. This case cooked in Indianapolis for years.

Lilly went on the market with growth hormone and they ended up selling Humatrope™ growth hormone. It was 190 amino acids long. Genentech sold Protropin™ growth hormone; it had 191 amino acids, and an extra "met" [methionine] from the start codon encoded by the synthetic DNA. We also made Nutropin™ and Kabi made Genotropin™, the met-less 190 amino acid growth hormone product using an *E. coli* signal sequence to make the product properly folded in the bacteria. It turned out that Lilly got orphan drug status under the Orphan Drug Act on their "met-less" growth hormone, and we could not get Nutropin™ on the U.S. market for seven years. So they were protected two ways, by UC's patent and by the Orphan Drug Act.

Lilly ended up being able to drag out the case more than seven years, so the orphan drug status ran out. Then Lilly settled and left Genentech with the UC suit. Of course the UC guys, as that case lasted quite a while, turned into rabid animals. UC sued Lilly on the insulin, and the Indianapolis judge said, "No, you don't have a case." Summary judgment, UC lost. They appealed to the federal circuit, and the federal circuit agreed.[1] So UC got nothing from Lilly on insulin, nothing. After that loss, UC went after Genentech. We can talk about that another time.

We could mention that Lilly really did a nice job with this tryp system. They pulled out all the stops. In five years human insulin was on the market, becoming the first product of this technology. I feel very responsible for it. I have a little niece who got diabetes when she was three, so she is taking human insulin that I had something to do with. So everything is really fine. A few VPs along the way started these legal battles.

Companies are like organisms. They're living, breathing organisms. In their life they fight against other companies for survival and food. The kind of character they have, how they go

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[1]Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559; 43 USPQ2d 1398 (Fed. Cir. 1997).

about their business, and the ethical standards of a company are very much dictated by the president; it's a top-down kind of thing. I think Bob installed a group of incredibly honest people here. Why we are in court all the time and being criticized is just unbelievable. Lilly, the same thing. They had a very ethical president and one of the senior vice presidents, Dr. Irving Johnson, was very helpful, though competitive. It was one of the other VPs who was trying to make a name for himself that started this suit. He had a little plan: Genentech won't give us rights to make growth hormone under their patent, so we've got to sue them. But, they kind of got carried away. When they lost, that VP was out of there.

Genentech Gains Early Credibility

Hughes: Was Genentech's association with a big pharmaceutical company early in its history a plus in terms of providing credibility in the eyes of the investment world?

Kleid: Oh, absolutely. It was extremely important, as you might imagine. We were molecular biologists making these bugs, but we had never done a clinical trial before; we'd never gotten anything through the FDA; we'd never manufactured anything. By working with Lilly, there was some cross-fertilization, just enough to make a go of it. Also there were some nice employees at Lilly whom we could work with. Some wanted to come to California. One was Bill Young. He was one of the first people to manage Eli Lilly's fermentation on the insulin project. He came to Genentech and helped us with growth hormone and other things.

The biotech start-ups absolutely had to have that relationship with a large company. We were the only company to really do that at that early stage, in the early eighties, and certainly in the late seventies. Very few companies decided they were going to be in the pharmaceutical business, and we really felt we were going to be the only one. We didn't know that all of a sudden everybody was going to copy us. We didn't know there was going to be Biogen and Cetus. What are they doing? Why are they even here? Then there was Genetics Institute. And they were all copying Genentech. They couldn't even think of original projects to work on. We were very fortunate to have these deals with major companies, especially with Lilly and Roche and Kabi. We were all hoping it was going to work. We worked together and it was very, very productive. Then the money started coming in, and then they sued us. [laughter]

Human Growth Hormone

[Interview 3: December 12, 2001] ##

Structuring the Contract with Kabi

Hughes: We're going on to the next Genentech project, which was human growth hormone. You told me last time that even before Genentech was actually working on growth hormone the company

signed a contract with Kabi.[1] Can you explain the thinking behind the contract when Genentech didn't yet have a project except in concept?

Kleid: I think it reflects the thinking of Bob Swanson that we had demonstrated a key thing with the somatostatin project: It was possible to make human proteins in *E. coli*. So the next step would be to make ones that had commercial significance, and one would be insulin and the second one that he and Herb Boyer thought about a lot was growth hormone. My understanding is, they believed that they could get companies interested in actually supporting basic research in developing a process to do something like that. Even though it hadn't been done before, maybe they could raise money to do the basic research steps. Normally, a company would be interested in supporting work at the final stages of development: Now that you know how to do it, let's get it ready for the clinic, and let's scale it up and do the real expensive stuff. But this was one step [forward]. We hadn't done a single experiment yet.

One of the imaginative things that Swanson and Boyer thought of was, well, we'll get these companies to support our work, but we know they will have a problem paying us money and then not knowing if the research project is going to work. So we will tell them, "You don't have to pay us a dime until we reach a benchmark, until we get to a certain stage. So your risk will be less. But then the benchmark payments should be pretty substantial because we have taken all the risks; we have gotten venture capital funding to do that small-scale first step." Then the company got its money back in the form of a benchmark payment.

They proposed that idea to Kabi and to Lilly at the same time. Tom Kiley was helping Bob Swanson design an agreement that had these benchmarks.

Hughes: Was there any precedent for working with benchmarks?

Kleid: Not that I had ever heard. At Stanford Research Institute, the contract was to carry out X, Y and Z. There would be no question that the details were [already] worked out on how to do that. The contractors were paying SRI to carry out X, Y, and Z. But here, we were asking to be paid to discover how to do the first step. If we didn't discover it, then we'd get nothing. I'd say that was a very new idea. So there was no money until we actually did it.

Hughes: What was Kabi's motivation in taking on a very risky venture?

Kleid: They were in the business of making growth hormone from cadaver pituitaries. They were a small company in Sweden that was interested in this technology. They thought genetic engineering would be really important in the future. They wanted to get a foot in the door.

Hughes: How had they learned of the technology?

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[1]Kabi is the result of a merger in 1971 of four state-owned pharmaceutical companies in Sweden--Kabi, Vitrum, Pecip and ACO. In order to develop competence in genetic engineering, Kabi started a biotech company named KabiGen in 1978 and placed the recombinant DNA growth hormone project with that new company. However, all the work done on the project in Sweden was done by "Kabi" scientists.

Kleid: I think through the scientific literature. It wasn't exactly a secret about the somatostatin project. They got a knock on the door from Bob Swanson. I think he knew somebody connected to this Kabi company or somehow got an invitation. He, and Herb Boyer I believe, went over to Sweden.

Hughes: Maureen McKelvey tells an interesting story from the Kabi side.[1] One of the Kabi executives was in this country in December of 1977.

Kleid: Bertil Åberg.

Hughes: I don't think it was Åberg. The way she tells it is, Hans Sievertsson was in this country, and he came by and talked with Swanson. Then at a later date an agreement was signed.

Kleid: Yes, they worked on that agreement during the time Dave and I first joined. So beginning February, March of '78, and then the agreement was signed in the summer of '78. My understanding is, the first trip to Sweden probably predated Dave and my joining the company. Then there may have been some visits during that period when our lab was just getting going.

Hughes: You told me last time that you weren't privy to whether these contracts had actually been signed, that you and Dave assumed that the contract with Lilly was all signed, sealed, and delivered. And it wasn't.

Kleid: That's right. My impression when I had that interview with Bob and Herb was that this was pretty much a done deal; we were going to be funded by these companies. Then I joined and found out, well, they haven't quite been signed yet. [laughter]

Hughes: How did that make you feel?

Kleid: Well, [pause] I can't recall right now. It wasn't distressing. There was nothing I could do about it except do my best to cope with that situation. We were not asked to help negotiate; we were not asked to develop any research plans. My previous understanding of contracts was that they were paying for service. It wasn't until after both these deals were signed that we found out that we were getting paid for benchmarks, and nothing if nothing worked out. That was quite different. In the Lilly agreement, the benchmarks had dates. If they weren't met then that benchmark would go away, and so would the contract. But the Kabi agreement was not like that; it did not have dates.

Deciding on a Semi-synthetic Approach

Kleid: Soon after the agreement was signed, we were given access to the first technical steps to be undertaken, the research plan. The first technical thing was to decide whether we were going to make the gene by cDNA or to synthesize the whole thing. Swanson wanted to have a little get-

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[1]Maureen McKelvey, *Evolutionary Innovation: The Business of Biotechnology*, Oxford: Oxford University Press, 1996. [SSH]

together with Boyer and Itakura and Art Riggs to try to decide which way to go. For a synthetic gene, this would be a huge thing, because it was about 190 amino acids. What's that, over 500 nucleotides I guess? Obviously I can't remember. It was going to be, I think, somewhere around 500 or 600 nucleotides long, so that would be more than ten times bigger than insulin. That would be a big project.

Hughes: DNA synthesis of the entire gene was doable, but unwieldy? Or was it more than that?

Kleid: Well, we weren't going to be able to clone the gene in one giant piece; we were going to have to design little pieces. With insulin, the B-chain was two parts--the first part and a restriction site. And then there was another part and another restriction site. So we cloned it in pieces, and it was reassembled. You would have to figure out restriction sites across this much larger gene. Then you would have to figure out the pieces you wanted to make. Then they would have to get synthesized. So it would be a huge planning thing that would take a long time to do. If we had the same problems like we had before with the insulin B-chain, then we needed to be very careful or we would end up synthesizing the wrong sequence. A mistake like that would make one piece virtually impossible, and I could see that we might go crazy trying to figure out what the problem was.

When I was told about the plan, immediately I came to the idea that we could use part cDNA and part synthetic. One issue with the cDNA was it had the signal sequence in front and there was no restriction site near the front, like that designed for insulin. Also, how were we going to put on a start codon, a methionine codon? We decided we didn't really want to try to make *E. coli* secrete anything at this point in time. We wanted to do it more like the insulin project, with these refractile bodies. So the idea was to synthesize the DNA encoding the front. We could design in a methionine "start" codon in place of the signal sequence, a nice convenient restriction site in front, and then synthesize the DNA down to the first restriction site that occurred in the cDNA.

All we needed to know was where was the first restriction site in the cDNA. The cDNA had already been cloned at UC Med Center by Howard Goodman's group, in particular by Peter Seeburg and John Shine. They had published papers on rat growth hormone, and they also had seminars on the human, which they had just completed cloning that summer. So all we needed to do was to figure out what that site was and then we could just synthesize the front. Then we could use the cDNA for the back.

Hughes: That scheme was your idea?

Kleid: There's a bit of debate because the main concept of the patent on growth hormone was a semi-synthetic gene, and the patent is by Goeddel and Heyneker. [pause] You don't think about what is the inventive concept when you're doing a project. I didn't even work on the project; I just helped organize a meeting where we talked about the approach..

I recall that the day we made the announcement on insulin down at City of Hope, we invited Keiichi Itakura and Roberto Crea to come back up to Genentech the next week. Heyneker was here from Holland to join Genentech, and we also had offered positions at Genentech to Peter Seeburg, John Shine, and Axel Ullrich. They were thinking very seriously about joining Genentech now that we had done this insulin thing. Heyneker had talked to those three, and

they were all going to join Genentech. Now that we had "finished" insulin, we could do the next protein, growth hormone.

In order to finalize the plan we had a meeting back at Genentech. At the meeting were Itakura, Roberto Crea, Herb Heyneker, Peter Seeburg, John Shine, Bob and me. (Dave Goeddel went mountain climbing.) Bob Swanson took very good notes about the program to synthesize the front part, and we even wrote down the sequence that we wanted to make. Shine and Seeburg knew where the restriction site was in the cDNA. The front would be synthetic DNA and then the rest would be cDNA. We drew up a little plan on the semi-synthetic gene idea.

Hughes: When would this have been?

Kleid: This was one week after the press conference.

Hughes: The press conference was on September 6, 1978. So maybe this meeting was mid-September.

Kleid: I think we were still in September.

I got this idea to make a synthetic part in front--we didn't call it a semi-synthetic gene. I first talked about it with Dave Goeddel, in the car riding to work just a few days after the growth hormone deal was signed. It was after the signing that Bob gave me some information about the growth hormone project and that we needed to figure out how best to go about it, cDNA or synthetic. Dave and I discussed the need to design restriction sites all the way down the huge gene, and instead we thought part synthetic, part cDNA would be better. I talked to Herb Boyer about it, and we sat down with Tom Kiley who had come up from LA. Kiley has some notes which predate Seeburg and Shine and Itakura and Crea and Heyneker coming to this meeting. The notes are dated in August [1978]. Then we had the City of Hope press conference, and then the meeting with these more fleshed-out notes written by Bob. In the first set of notes (with Boyer and Kiley), we didn't know what the cDNA looked like; we didn't know where there would be a restriction site.

Hughes: Because it hadn't been published yet?

Kleid: They had published it in the proceedings of a meeting in Scandinavia, the Benzon Symposium. At the Benzon Symposium, Howard Goodman gave a talk on the rat growth hormone and his progress so far with human growth hormone. They published at the meeting this swatch of the DNA sequence data encoding part of human growth hormone. It wasn't the whole thing. In fact, the first paper was about a cDNA clone that was missing the front. It had no DNA encoding the signal sequence or the first 24 or so amino acids. We knew about where the front would be because everybody knew what the amino acid sequence of growth hormone was. So we were able to make a complete plan, to go ahead and synthesize the front, go to this first restriction site, and then use cDNA for the rest.

Peter Seeburg and Axel Ullrich Agree to Join Genentech

Hughes: Was the assumption that Genentech was going to do its best to attract these three UCSF postdocs?

Kleid: They were happy with the salary they were offered. They were offered some shares in the company if they came. They were interviewed by Herb Heyneker and Swanson.

Hughes: When?

Kleid: The September, October 1978 time frame. Before that September growth hormone meeting, they had decided they were going to come. As it turned out, over the next few months John Shine's wife really wanted to go back to Australia. Try as he could, he could not convince his family that he should stay longer in the Bay Area. So he decided not to come. Ullrich wanted to do some more work at UC, so he didn't actually join Genentech until January of '79.

Seeburg had a very difficult time in this period of September, October, and November. He decided to leave UC, but he still wanted to stay, still wanted to do work with John Baxter on growth hormone. He wanted to come to Genentech but he wanted to have a little bit of both worlds, and he was very confused at what he should do. At that particular time the lab at Genentech wasn't big enough to hold him anyway. There really wasn't any place for him to work. The place was being built, and it actually got finished enough to have a place for Seeburg and Ullrich in early January 1979. But in the meantime there was really no space. Seeburg kind of wanted to stay at UC, and he kind of wanted to come to Genentech, and we really wanted him to get started on the growth hormone project because this was going to be his project.

Hughes: What was Seeburg's motivation in moving from academia into a promising, but risky company?

Kleid: I think the main one was that he would actually be able to make a product for this disease. His position at UC was a postdoc paid by Europeans, so at some point he'd have to find another job anyway, whether it would be that year or the next year. So he thought that this would be a good thing to do, but he was horribly ambivalent about it.

On top of that, Seeburg was having troubles at home. He had a girlfriend at the time, and he hadn't separated from his wife. The girlfriend lived in the same building he was living in. He had two little kids and a wife from Germany. He was "separated" but his wife still washed his clothes. He would come to work after several Irish coffees in the morning. He got in a big argument with Howard Goodman about how much of the project was going to go with him to Genentech and how much was going to stay behind. They were interested in sequencing the whole gene for growth hormone, so there were some very major research questions that were obviously going to generate lots of publications, as well as this practical application of let's <u>make</u> some growth hormone. UC at that time was not that interested in actually making drugs. That's really out of their bailiwick, but they were very interested in contributing.

Competing Genentech and UCSF Research Programs

Kleid: Howard Goodman also was made an offer to help Genentech, to have a position not unlike Herb Boyer's where he would add his expertise to the company. Swanson was very interested in having another professor be part of the company. But there was a falling out there. Dr. Goodman wasn't quite happy that he didn't have as many shares as Herb Boyer did. They both had some discussions with Bill Rutter, who was the chairman of the UCSF biochemistry department, who was kind of frowning on the whole thing at that particular time, rather a new experience. So the Goodman connection kind of fell off, and the Genentech end kind of took off.

Then Howard Goodman went to Lilly to see if Lilly would be interested in growth hormone, and they were. So Eli Lilly decided that they would support Howard Goodman's program on growth hormone, which he joined up with Baxter. Bill Rutter, and a group at UC Med Center called the Hormone Research Institute, with C.H. Li, was also part of this complex equation.[1] They had gotten the amino acid sequence for growth hormone from the protein. So here were some rather powerful groups in 1978: Goodman and Baxter, supported by Lilly, and also Rutter and Li, whose Hormone Research Institute was being supported by Hoffmann-La Roche.

Hughes: How was Hoffmann-La Roche in the picture?

Kleid: They had something to do with chemically synthesizing amino acid sequences. They had done something with C.H. Li, and also they supported the work of Merrifield, remember the solid-phase synthesis of amino acid peptides where you have a particle and you synthesize peptides that are joined onto that? Hoffmann-La Roche was involved with that project. Hoffmann-La Roche was interested in the synthesis of peptides.

Hughes: Do you know when Lilly began to support the UCSF groups?

Kleid: It was in '78. What Howard Goodman had done was to sign up Peter Seeburg and Ullrich to work on the Lilly growth hormone project and the Lilly insulin project. They had signed little confidentiality and consulting agreements with Lilly. So here's Peter Seeburg coming to Genentech having signed a consultancy agreement to help Lilly on growth hormone, but he's going to Genentech to work on Genentech's project. We didn't really know anything about that.

Hughes: Really?

Kleid: At the time we knew nothing. We did not know that there was any real interest between Howard Goodman and Lilly. It turned out that Howard Goodman talked to Lilly about the human growth hormone cDNA and rat insulin cDNA. So there became, unbeknownst to most of us, a competition to see who could make human growth hormone in bacteria first, Genentech or UC-Lilly. As it turned out, Genentech won that race in very short order when by the summer of '79 we had chemically synthesized the front part of the gene.

Seeburg still was having trouble with acclimatizing to Genentech and didn't really come to work at all. Nothing was happening. So here we had this agreement that we would accomplish

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[1]For the interrelationships of Rutter, the Hormone Research Institute, and Li, see the oral history in this series with William J. Rutter. [SSH]

these benchmarks. In 1978 there was a time line that Bob Swanson wrote up and gave to the Kabi people, saying, "We're going to make this amount of progress by this time and this amount of progress by that time. We decided we are going to do the gene by part cDNA and part synthetic. We've got the people to do this." Then the date in early 1979 came around when he said we were going to do it and nobody had started on it yet. Seeburg was still goofing around.

Preparing Messenger RNA

Hughes: He was supposed to take care of the cDNA portion?

Kleid: Right. The idea is that we will make our own cDNA clone. UC has theirs and we're going to make ours. So we contact Kabi about getting samples of cadaver pituitaries so that we can make cDNA. We got these pituitaries and we start prepping, making these mRNA samples and trying to clone the cDNA. We were trying to find a source of messenger RNA so we could clone the cDNA. You isolate messenger RNA, reverse transcribe it into one strand of DNA, and then make a second strand. So you end up with a preparation that is a double-stranded copy of a messenger RNA. But your starting material is a huge mixture because it's all the messenger RNA from the pituitary. The pituitary samples turned out to be not a very good source of messenger RNA because they weren't kept properly. When you take out the pituitary, what you want to do is immediately freeze it. If you don't, then over a few hours the enzymes in the cells starts chewing up the mRNA and you just get pieces. So it turned out we weren't able to make very good mRNA preps from pituitaries.

Well before 1978, Peter Seeburg, well before he left UC, along with Joseph Martial in Baxter's lab, had gotten their pituitaries from operations right at UC Med Center. They had a program with a surgeon that when he took the pituitary out he would drop it in liquid nitrogen.

Hughes: That was probably through Baxter because Baxter was an MD.

Kleid: That's right. Even before Seeburg came to Genentech in the summer of '78, they were getting these purified pituitaries. Because of the NIH guidelines, in order to clone something out of a human sample, they had to make whatever they were cloning 99 percent pure. How they would do that is they'd scale up that procedure to make a huge amount of messenger RNA, copy that into double-stranded cDNA, and cut the cDNA in about half with restriction enzymes.

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Kleid: They then separated the cDNA using electrophoresis and purified the two cDNA fragments from acrylamide gels and then linked the two back together again. So they would get two pieces, one from the front part, one from the back part, purify these, join them together, purify them again on the gel, so they could get this one very pure piece of mRNA that had been double-stranded cDNA. It was cDNA encoding codon 24 to the end, plus some from the untranslated region. Before they cloned that re-joined cDNA, they took their data to UC's biosafety committee and said, "We have purified this piece of cDNA to greater than 99 percent purity. We want to clone it." They said, "Okay--it looks pure enough to us." So they were

allowed to clone that piece, and they carried out that work. It was this human growth hormone cDNA (the one that was missing the front part) that was discussed at the Benzon symposia and that was later claimed in a University of California patent application.[1]

In the meantime, Drs. Seeburg, Baxter, and Martial said, "Well, what we really want to do is to make a clone of the whole thing, with the signal. We want to see what the signal sequence is and what the rest of this is." So they took a sample of messenger RNA and they converted it to double-stranded cDNA without cutting it with restriction enzymes and doing the purification step, and then put it in a little ice bucket and took it to France. Under the auspices of Eli Lilly, which had a laboratory in France, they cloned the full-length cDNA for human growth hormone.[2]

Hughes: This was to avoid the NIH guidelines?

Kleid: Exactly. Because the guidelines said if you're going to clone human DNA it has to be 99 percent pure, and of course this particular prep would not be. It would be perfectly safe; there's nothing wrong with that experiment. But they couldn't do it in the U.S., so they did it in France.

Hughes: Who is *they*?

Kleid: Martial, working with Paul Burnett, the scientist from Eli Lilly who went with him and set up this lab in France. I think they even did the next to the final step at UC (the ligation), so it was only the last step they had to do: transform *E. coli*, pick colonies with a growth hormone cDNA clone, and bring the colonies back. So they found a colony that had a clone and took it back. Actually, I think the way it really went was that they had only one that was okay and brought that back at UC. So they really just did one tiny little step in France, which was the transformation step, and they did everything else at UC.

Hughes: Seeburg didn't go to France?

Kleid: No. But Seeburg had helped make all the materials to do that. Now, Seeburg always used to say that he did the whole thing at UC, <u>even</u> the transformation and <u>even</u> finding the plasmid. I don't know what the story is.

Hughes: When did he tell you that?

Kleid: In the '79 time frame, that they had done it all at UC. Martial has notebooks that were from his time in France. I have no reason to doubt them or him.

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[1]It was this cDNA that Dr. Seeburg brought to Genentech that was later the object of a controversy as to whether or not Dr. Seeburg used DNA from this clone in Genentech's work or whether another clone that Dr. Goeddel had made was used at Genentech. *See discussion below.* The cDNA was the subject matter of United States Patent 4,363,877. Genentech's study was published as Goeddel et al., *Nature* 281, 544 (1979).

[2]This cDNA was used in the publication: Martial et al. *Science* 205, 602 (1979).

Hughes: Why would Seeburg tell you that?

Kleid: I don't know. Their paper on growth hormone got published close to the same time as Genentech's.[1]

The Growth Hormone Clone Controversy and the UC v. Genentech Trial, 1999

Hughes: One more thing about Seeburg, which must have come up in the recent UC v. Genentech trial: The accusation was that after he had arrived at Genentech, he went back to UCSF on New Year's Eve 1978 and took the human growth hormone clones from Howard Goodman's refrigerator and brought them back to Genentech. UC's later claim was that they were the clones used in Genentech's production of human growth hormone. Do I have it right?

Kleid: That's the story that Seeburg gave about himself at the trial, but it wasn't the story as it happened, and it wasn't the story that he testified to before that time. I'll tell you the real story.

As I understand it, there was a trip that Ullrich and Seeburg made to UC to obtain the samples that they had been given permission to bring to Genentech. Baxter, Goodman, and Seeburg had arranged it. Seeburg and Goodman would divide up the project on the research level, and they would do part at Genentech and part at UC. To carry out that project Dr. Seeburg was allowed to take the sample of the partial growth hormone that was cloned at UC, but not the full-length. Dr. Goodman told him, "I'm not going to let you take the full-length one. That's going to be part of our project with Lilly." As far as I know, that's exactly what Dr. Seeburg did. He did not take the full-length one, but he did bring the partial one. He had it at Genentech, as far as I understand, and that's what he said.

Apparently, Drs. Ullrich and Seeburg were at some party and they decided that they would then go get the samples of restriction enzymes, buffers, mRNA preparations, and some cDNA clones. So on New Year's Eve they did. According to their own testimony, they went to UC and they got samples of reagents for the most part. Dr. Ullrich also took little pieces of cDNA for insulin that he had made which he wanted to study some more, although we had synthetic DNA for insulin at Genentech. We had no need for cDNA pieces or anything like that.

So they brought these reagents with them for their own study to continue on their work with UC. In fact, they have four or five publications with their UC professors after arriving at Genentech. They continued doing basic research at Genentech that was not related to Genentech's commercial stuff. Of course the UC trial never mentioned that Seeburg while at

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[1]Joseph A. Martial, Robert A. Hallewell, John D. Baxter, Howard M. Goodman, "Human Growth Hormone: Complementary DNA Cloning and Expression in Bacteria," *Science* 1979, 205:602-7 (August 10); David V. Goeddel, Herbert L. Heyneker, Toyohara Hozumi, Rene Arentzen, Keiichi Itakura, Daniel G. Yansura, Michael J. Ross, Giuseppe Miozzari, Roberto Crea, and Peter Seeberg, "Direct Expression in *Escherichia coli* of a DNA Sequence Coding for Human Growth Hormone," *Nature* 1979, 281: 554-8 (October 18). [SSH]

Genentech continued to do research and publish with his old boss Dr. Baxter.[1] They were perfectly good friends, and they worked together for at least a couple of years. Now it's all become sinister.

Genentech had a deal with Kabi that we would create a gene for growth hormone at Genentech. We didn't have an agreement that said that we were going to take UC's clone and give it to Kabi. That's ridiculous. Dave Goeddel was making the cDNA from the Kabi pituitaries. As I told you, the Kabi pituitaries weren't working out so well. It turned out that Seeburg not only brought samples of the clone, but he also had leftover samples of mRNA extracted from pituitaries at UC Med Center. This was mRNA that was now ready for the trash, because they had already cloned the full-length, and they had already cloned the piece, so this was going in the garbage. So side-by-side were samples from Kabi, Dave Goeddel made cDNA from the mRNA from the UC Med Center pituitaries, and that's in our publication. The very last line says, "mRNA provided by Peter Seeburg from UC Med Center."[2] No one ever disputed that we got the mRNA from UC Med Center and used that to make the cDNA.

But here we come to this 1999 trial and we look in Dave Goeddel's notebook where it shows, "Here's my double-stranded cDNA. Here I am cutting it out of the gel. Here it is all cut, ready to clone. Give sample to Seeburg so he'll cut it with this particular enzyme. Gave sample to Seeburg. Seeburg gives the sample back, and it is cut." Then Dave clones it, and then we make our new clones of growth hormone. Well, the allegation is that when Dave Goeddel gave the sample to Seeburg to cut, Seeburg secretly switched that sample with his own UC sample, and then gave Dave Goeddel the UC sample of DNA, not the Genentech sample that Dave gave him cut.

Hughes: What would be Seeburg's motive?

Kleid: At the 1979 time frame--<u>none</u>. It's completely made up in 1999 by the attorneys for UC in order to make the jury not like Genentech in order to get more money awarded to UC. Just think about it. Dave spends all this time, weeks, finally getting this sample of double-stranded cDNA exactly the way he wants it. There's a particular restriction enzyme that Seeburg has, so Dave gives the sample to Seeburg, Seeburg cuts it; Dave gets it back and continues on with the experiment. In Dr. Seeburg's depositions leading to the UC case, Seeburg says exactly the real story, exactly what happened: the messenger RNA came from UC. Dave made the double-stranded cDNA, we cloned it at Genentech.

Now at the trial Seeburg says, "Oh, yes, we cloned it at Genentech, but by that I mean we made more copies of the original UC clone, but I forgot to mention in my deposition that I made this switch." In Dave's notebook it shows that Dave gave it to Seeburg and Seeburg gave it

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[1]Fiddes et al. *Proc. Natl. Acad. Sci. USA* 76, 4294-8 (1979), Roberts et al *Proc. Natl. Acad. Sci USA* 76, 2153-7 (1979), Martial et al. *Monographs Endocrinology* 12, 279-89 (1979), Baxter et al. *Recent Prog. Horm. Res.* 35, 97-153 (1979).

[2]A line in the conclusion of the publication co-authored by Dr. Seeburg reads: "RNA used was prepared by P.H.S. while a postdoctoral fellow in the Department of Biochemistry and Biophysics, University of California at San Francisco." Goeddel et al *Nature* 281, 544 (1979).

back. The attorneys for UC argued that Dave Goeddel was in on the switch because he failed and couldn't repeat making the clone described in the Goodman patent. According to them he was a bad molecular biologist and a cheater. That's just ridiculous. So what does Seeburg do at the trial? He says, "Dave was in on it. Dave knew that I switched this. He failed to make a good cDNA clone, and I switched it and he was in on it. Our publication is somewhat incorrect. We really used the clone I made at UC." That was just absolutely outrageous!

Hughes: So Seeburg's explanation for making the alleged switch is that his cDNA was better than Dave's?

Kleid: The lawyer's explanation was that Goeddel failed and Seeburg had to come to his rescue to save him from some sort of embarrassment. Bunch of crap! And this is from this guy Jerry [Gerald P.] Dodson who was the attorney for UC, the attorney on this case for almost a decade. He kind of made a career out of badmouthing Genentech. I hate this guy. He is a disgusting attorney. To make up this story and then convince Seeburg over years of talking to him, "Why don't you just say that you switched the samples because nobody will ever know." So at the trial, this is the first time Seeburg ever says, "Yes, I switched them." If you read the transcript it's very hokey. It's <u>totally</u> unbelievable. In the end the jury discounted the whole thing.

Hughes: Why would Seeburg accept Dodson's suggestion? What would be his motivation?

Kleid: His motivation would be there's a patent and the inventors are Seeburg, Shine, and Goodman--U.S. Patent 4,363,877. UC has an agreement that if you are an inventor on a patent you get to share in the royalties. So his motivation was hundreds of thousands of dollars. I don't know exactly how much--maybe even a million dollars to his own personal pocket. During the trial, UC was asking for royalties and punitive damages. They wanted $1 to $2 billion from Genentech because of this switch and because they claimed that they had a patent on a part of the growth hormone gene and Genentech was infringing. Their claim says, "If you use this particular section of the DNA of growth hormone, then that infringes our patent. If you make, use, or sell anything that used this piece of DNA, then you owe us royalties." The allegation there was, we were using that piece of UC patented technology in our manufacture of growth hormone. Instead of synthesizing the whole thing, which we could have done, UC says we're infringing their patent, which they had since 1982. The life of a patent is 17 years, so according to them, we owed them for all of that time.

UCSF's Patent

Kleid: In '78 Howard Goodman with Shine and Seeburg filed a patent application with UC on growth hormone with this swatch of growth hormone cDNA. (This application became U.S. Patent 4,363,877) They filed a lot of other patents, too. Goodman and Rutter filed patents on insulin and other things. UC has this agreement with Lilly that says that Lilly has the option to license these patents down the road if anything becomes useful.

Hughes: An exclusive license?

Kleid: Exclusive license. Lilly has an option for an exclusive license. The agreement doesn't say anything about when they have to exercise this option. As it turned out, they didn't exercise the option for years, until the late eighties. Lilly finally finished the human insulin project with Genentech's technology, not UC's, and then wanted to do growth hormone, but Genentech had the patents on growth hormone--except for this UC-Goodman patent on this swatch of cDNA. One of the problems with the Goodman patent is that the DNA sequence they had determined and patented was wrong. So they had patent claims on a piece of cDNA that was a mutant. So the patent claim was completely useless. The cDNA sequence Genentech used wasn't patented--we didn't use the sequence that was in the Goodman patent.

At Lilly's behest, and with the help of some attorneys out here in California, UC convinced the patent office that there was a typo in the claimed sequence. So they fixed the sequence data and submitted something called a "certificate of correction" where they told the patent office, "We made some typing errors and we have to change the sequence. Anyway, the real plasmid is deposited, and you can go to that plasmid and read the sequence."

Hughes: What happened when they did that?

Kleid: Well, the plasmid that was deposited turned out to be for rat growth hormone. They hadn't deposited the right thing.

Hughes: Was it just one wrong nucleotide?

Kleid: No, it was like three places. It wasn't the whole sequence anyway; it was just part of it codon 24. So we said, "This patent's useless." In the mid-eighties, the Lilly attorneys convinced attorneys at Ciotti and Murashige, in fact Ms. Kate H. Murashige in particular, to submit a certificate of correction. Even though she had never worked on this patent and the patent's been issued for five, six years, she submitted a certificate of correction and explained that it was just typos, although she had no idea.

It turns out that when they wrote the patent, they read the sequence data from the Maxam-Gilbert sequencing gels and then compared it to HCS, human chorionic somatomammotropin, that Dr. Shine had sequenced about a year earlier.[1] So now they were doing the sequence for growth hormone, and they were reading the sequence off and comparing it to the sequence of HCS which is quite similar. The incorrect sequence of hGH cDNA that was in the Goodman patent application was handwritten on a copy of the publication about HCS.

That particular copy of the paper got sent to the attorneys for UC. The attorney took that information and constructed the DNA sequence data figure that is in the Goodman patent application and from that wrote the claims to the incorrect hGH cDNA sequence. When he prosecuted the application, he sent his copy of this very same HCS paper to the patent office, and the copy that he sent is the one with the handwritten stuff on it. So in the file history of the Goodman patent 4,363,877 is this HCS paper with the incorrect human cDNA sequence handwritten on it. Every single error that's in the sequence is in places where Shine, Goodman and Seeburg didn't notice there was a difference between growth hormone and HCS. So it

[1]Seeburg et al. *Cell* 12, 157-65 (1977), Shine et al. *Nature 270,* 494-9 (1977).

wasn't typos at all; that was the data they had at the time. There's a patent office rule that says you can't change the data in a patent years later. Your data is your data; you have to live with that. But they said no, it was typos. But Ms. Murashige didn't know the story as to where the data came from. She just told the patent office it was typos.

More on UC v. Genentech, 1999

Kleid: We filed motions on this issue with the judge in the UC vs Genentech case, saying you're not allowed to change the sequence data with a certificate of correction. He denied that motion and refused to let us talk about that at the trial. He prohibited us from bringing that issue up with the jury. He said it's a summary judgment; he'd decided on it. If you have any problem with that you take it to the appeals court.

Hughes: This was Charles Legge?

Kleid: Right. In fact, he granted several motions brought by UC in that case that pretty much wiped out most of our defenses, and so the trial became infringement under the doctrine of equivalents. The cDNA in the 4,363,877 patent not only had the human growth hormone cDNA sequence wrong, and was only part of the cDNA anyway (codons 1-24 were missing), but it also had some stuff beyond the end of the growth hormone cDNA sequence. UC claimed the whole piece. We didn't use part of it so we didn't literally use the piece of cDNA UC claimed. So the case became one of doctrine of equivalents: Did we use the equivalent of their cDNA piece in our cells that make human growth hormone? Nowadays, you wouldn't be able to bring that claim. There are new laws saying that if you modify your claims you can't use doctrine of equivalents. If the trial was today it wouldn't even make it that far.

Judge Legge cut out all of our major defenses and left us with just one single defensive claim, no infringement under doctrine of equivalence. The burden on UC is called "by preponderance of the evidence," which means more likely than not. Whereas our defenses, which were about invalidity, had to be by "clear and convincing evidence." But those invalidity issues were all gone by granting UC's summary judgment motions. In order to knock out a patent because it's not valid, it has to be by clear and convincing evidence. We never got a chance at trial to even argue that.

Judge Legge decided that none of our invalidity evidence was clear and convincing and threw it all out, so we were left with only the non-infringement defense. We didn't literally infringe, but there was nothing we could do about doctrine of equivalents. Our defense to the allegation that we infringed under the doctrine of equivalents was that our clone had the whole sequence plus a methionine start codon, and we could use that plasmid to actually make growth hormone. Their clone only had a part, codon 24 to the end, and then some more on the end, and it was useless for making hGH. It was not equivalent because you couldn't use it to make growth hormone. The judge refused to allow us to make that argument.

Hughes: Do you think there was some problem with lack of scientific understanding?

Kleid: Well, there always is some. My feeling was the judge wanted the case out of his court with UC winning. It was the university against Genentech. They didn't really have a decent patent, but "What the heck? I'm going to let them out of here with a patent."

There's one level beyond district court, which is the Court of Appeals of the Federal Circuit [CAFC]. The court of appeals would look at all the summary judgments and every decision that the judge had made, and we would have a second bite at all of these different issues. But in Judge Legge's district court, in the courtroom trial, he would only allow one issue, doctrine of equivalents, and we were not allowed to argue that our plasmid works and UC's doesn't. He dictated the result in that trial. He basically said, "If the some of the nucleotides from UC are in Genentech's plasmid, then Genentech infringes. It's equivalent." So it was extremely difficult.

Then layering on this was this lie from Peter Seeburg. From the first day we didn't have a chance. It ended up being a hung jury. One juror refused to go along with the judge's instructions. He said, "I don't think this is infringement." The judge's instructions were, "If the nucleotides are in Genentech's plasmid then that's equivalent." The juror refused to go along with that. When they interviewed him after the trial, his answers indicated that he didn't go along with the judge's instructions.

Hughes: On that point?

Kleid: On that point. So, "I don't find infringement." But if he had listened to what the judge ordered him to consider, then he would have been forced to find with the rest of the jurors.

Hughes: Why did Genentech decide to settle? Could you not have asked for a retrial?

Kleid: There was going to be a retrial, and we were going to have to do this again four months down the road, bring in all these witnesses again, do this whole shooting match all over again. The judge certainly was not going to change any of his pretrial rulings. It would be exactly the same thing. Maybe that one juror wouldn't be there, then we would lose. Then we would go to the CAFC.

The prospect of that, think about it. The publicity that surrounded that trial depicted, here's wonderful UC and the mean and nasty Genentech thieves. That's what the papers were all about. We would have to drag all the way through that again. And if the judge got his way we would be found guilty now, and then we'd have to go to the CAFC, and then of course everything would have been reversed in our minds.

Throughout the growth hormone project there was some contribution from UC to Genentech's project, which was the mRNA, the knowledge of where the restriction sites were, and Seeburg coming. There was a contribution from UC to our project, but it wasn't worth a billion dollars.

Actually, there was an earlier disagreement with UC. When the growth hormone papers were originally published in 1980 there was a huge brouhaha over that messenger RNA. We made an agreement with UC and paid them for all the materials. It was several million dollars.

Hughes: On this same point?

Kleid: Exactly the same point, except for one twist. In those days we were paying for the mRNA, and here in the recent case the allegation is we stole the DNA. The earlier disagreement was not about patent infringement. The UC patents hadn't issued at that point in time.

UC-Lilly Agreement, 1980s

Kleid: One other thing about that particular patent: UC and Lilly made an agreement in the mid-eighties. UC went to Lilly and said, "We want you to license our insulin patent and our growth hormone patent. Actually, we want you to look at all of our patents because now you're in the insulin business; you're in the growth hormone business. It's time you exercised your options or not. So Lilly said, "All right, we will look at all this insulin stuff and this growth hormone stuff." They came back and said, "We're pretty interested in insulin, but right now, let's do this: We will license this Goodman growth hormone patent and give you a royalty of 4 percent for an exclusive license. But, since we paid for the research, it's only going to be 2 percent. But, we are making this deal if and only if you sue Genentech under this Goodman patent. If you don't sue Genentech under the Goodman patent, you get nothing." That was the deal. UC said, "Okay, but we're going to do this insulin deal?" Lilly said, "Sure, we're going to do the insulin deal, but you sign this one first." So UC signed the deal that dictated that UC would sue Genentech, thinking that Lilly was now going to license the UC's insulin patent which were much more valuable because human insulin had much larger sales. But then Lilly stiffs them on that, and UC is also forced to sue Lilly on UC's insulin patents.

Hughes: You talked about this.

Kleid: After that suit ran its course UC lost. Lilly was found not to infringe because UC's patent was found only to cover rat insulin, not human. So UC gets paid nothing on insulin. Lilly pays a very tiny royalty on growth hormone, but now they've sicced this UC mad dog onto Genentech, because now we're the only ones that have any money that they can get. So Genentech, after this UC v. Genentech trial,decides to settle. The settlement was a reasonable royalty around the same range as Lilly's royalty for the life of the Goodman patent, which was running out then. The trial ended about the same time that patent expired. So 2 percent times all the money we made on growth hormone ended up being the settlement. So it wasn't so bad. We would have probably done that in the beginning, but because of the Seeburg story, UC was going for big damages, way, way beyond reasonable royalties.

Hughes: What a story.

Kleid: [sighs]

Hughes: Is it over?

Kleid: Well, I don't think anything is ever over.

Current Growth Hormone Marketers

Kleid: There are now five companies in the growth hormone market. There's one very strange coincidence. Genentech made its own growth hormone gene, I swear to you. Lilly got its growth hormone gene from Martial and Baxter. They ended up using the full-length one and developing it for growth hormone. BTG, Biotechnology General, the other competitor, got their gene from Seeburg's friend who went to Columbia University in New York. Seeburg was working at UC Med Center, and John Roberts[1] brought the clone with him and was studying it there. BTG claims that they got the clone with "no strings attached."

Novo Nordisk tried for a very long time to clone the cDNA. They were trying and trying, and then this guy makes a trip, comes back; all of a sudden it's in their strain collection. That cDNA clone is from UC also. It is exactly the same one. Serono, the fourth Genentech competitor, got a hGH cDNA clone that was originally worked on at Celltech, which it got from Dr. Hamer at NIH, who in turn got it from Peter Seeburg while at Genentech.[2]

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Kleid: Peter collaborated with the people at NIH who made growth hormone using vectors designed for tissue-culture cells, for mammalian cells. That project was worked on at Celltech and then eventually went over to Serono. That gene is said to come from Seeburg's work at UC. So it's funny that of five competitors, four get their gene from UC. It's only Lilly pays anything on that. Genentech's gene, we made ourselves, yet we're the ones accused of stealing the gene from UC! Is that incredible?

Hughes: It's quite a story.

Improving Expression: The Tryp Promoter and Other Methods

Kleid: There's one more area of growth hormone to discuss. In Genentech's project with growth hormone, the first product we made was Protropin, which has a methionine on the front of the growth hormone. That one used the same vector system that we used for insulin. In other words, it had the tryp promoter, and it makes a huge amount of growth hormone when it is induced. So you grow the bacteria under conditions where the tryp promoter is turned off, and then you switch it to conditions where the tryp promoter gets turned on, and the bug starts filling up with growth hormone. It makes those refractile bodies just like those that I showed you in that picture for human insulin. Ten- or 15 percent of the *E. coli* total weight is this precipitated, denatured, growth hormone. This is then recovered, and then it needs to gets refolded.

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[1]Roberts, JL. et al. *Proc. Natl. Acad. Sci USA* 76, 2153-7 (1979).

[2]G.N. Pavlakis, N, Hizuka, N, P. Gorden, P. Seeburg and D.H. Hamer, *Proc. Natl. Acad. Sci USA* 78, 73980402 (1981).

Hughes: Was the tryp promoter unique to Genentech?

Kleid: We filed a patent on using that in this kind of system. The sequence of the tryp promoter and how it works was mainly Charles Yanofsky's project at Stanford. But to use it in this particular way, in a commercial sense, was patented by us.[1]

I just want to tell you that the plasmid that we made Protropin™ from all those years was one that I made with my own hands. So the infringing article in the UC vs Genentech case was a plasmid that I made.[2] And the infringing article in the UC vs Lilly case on human insulin was also one that I made.[3]

Hughes: This is recorded in your notebooks?

Kleid: Yes. The insulin plasmid was the human proinsulin. Originally we did the A-chain on the end of beta-gal and the B-chain on the beta-gal. Then we shortened the gene so it was this little tiny piece of the tryp and then the A-chain and B-chain. The amount produced in *E. coli* was huge. Then the third version of it was this little tryp promoter, a little fusion protein, and a human proinsulin cDNA, that was part synthetic and part cDNA. And that was Lilly's second-generation human insulin production process where they were able to make human insulin all in one cell. When they first started marketing insulin, they made it [in] two different bacteria and recombined to form it.

Hughes: That was a second expression system that you sent to Lilly?

Kleid: Yes. In fact, I sent them all at the same time. The human insulin A-chain, the B-chain, and proinsulin we sent the same day in April of 1980. The first ones they used for several years, and then in the mid-eighties they switched over to proinsulin and developed a process to re-fold it and cut out the C-chain. That took a long time to develop. And that was the product that was the infringing article in the UC-Lilly case.[4]

Hughes: Can you explain why the proinsulin method is presumably superior, if Lilly moved to that eventually?

Kleid: You know, I never actually understood why it was superior. The only issue would be, could they make it cheaper. In the A-chain and B-chain method, you make the A-chain in one bacteria, purify the fusion protein, and clip the A-chain off with cyanogen bromide and purify the A-chain. In the other bacteria you do exactly the same process for B-chain. So you have

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[1]US Patent 6,333,174, D.G. Kleid, H.L. Heyneker, D.G. Yansura and G.F. Miozzari.

[2]US Patent 6,333,174 Example II.

[3]European Patent Application EPO 055945, D.G. Kleid, D.V. Goeddel and R. Wetzel.

[4]University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir 1997).

this pure A and pure B ultimately derived from those insoluble bodies.[1] Lilly developed a very nice method for recombining them into insulin.[2] Then, if the chains didn't completely recombine, of recycling improperly associated A-chain, B-chain.

In the proinsulin approach, you'd chop it with cyanogen bromide. Then you refold that as a chain. Maybe there's a higher yield to that. But then you have to junk it up by adding an enzyme that cuts out the C-chain. Then you have to purify it again, so it needs another new reagent, this protease. In fact, Lilly ended up cloning the protease gene to make a lot of this protease in order to add to this process. There was a scientist there named Ron Chance who developed all this.[3] It's very elegant peptide chemistry. So they decided to go with that. I'll speculate that the amount of money they saved going from one method to the other probably wasn't that much. But it was enough to engender this suit from UC, because now they supposedly infringed this patent by using a mammalian proinsulin cDNA sequence. So they had to fight that patent, which cost them quite a bit, but in the end there was no infringement because the patent couldn't cover human.[4]

Hughes: Dave Goeddel told me that he began to work on the growth hormone project in February of '79 because he perceived that it was not going well.

Kleid: It was not going at all. Dave was focusing on the synthetic gene, the first part. Itakura was doing fine on his part; he was working very hard on that, and we were getting the synthetic gene. And Dave and Herb Heyneker were working together to clone the synthetic part. The cDNA part is what was not going at all, and that was going to be Seeburg's project.

Hughes: Was there nobody else at Genentech who could deal with the cDNA component?

Kleid: Well, there were only five of us. There was Dave and I and Herb Heyneker--

Hughes: Didn't Heyneker have that capacity?

Kleid: He hadn't done cDNA either. Ullrich joined in January along with Seeburg, and Ullrich was more interested in the insulin and proinsulin projects.

Hughes: Yes, because that's what he had been working on at UCSF, of course.

Kleid: There was kind of a separation of labor between growth hormone and insulin. As I said, from the beginning, Seeburg was coming to continue to work on growth hormone. He still had a project with UC. He was very interested in the gene for growth hormone, in other words how

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1D. C. Williams, R.M. Van Frank, W.L. Muth and J.P. Burnett *Science* 215, 687-9 (1982).

2U.S. Patent 4,421,685 Ronald E. Chance and James A. Hoffmann.

3R.E. Chance and B.H. Frank, "Research, development, production and safety of biosynthetic human insulin." *Diabetes Care*, Suppl. 13, 133-42 (1993).

4University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir 1997).

the human gene is organized, and he wanted to do the sequencing of that. He proceeded to do that.

It turned out there was not only growth hormone but there was HCS; there were three HCS genes, and then there's something called growth hormone variant. So there are five genes along the chromosome, all in order, all these closely related structures. So Seeburg ended up sequencing the whole thing over the next few years. As I said, he had collaborations at NIH and at NYU, and which chromosome the gene is on.

The number of publications that Seeburg has on growth hormone is staggering. He becomes by the time he leaves Genentech almost the most cited scientist in the world. Because he was interested in sequencing, he set up a group at Genentech to do DNA sequencing, dedicated to methodology for sequencing. Everybody that had a gene gave it to Seeburg's group, and they did the sequence of it. But in trade for that he put his name on the paper. So he has his name on every major paper out of Genentech. [chuckles] *Current Contents* keeps track of citations, and Seeburg's name shows up being cited almost more than anybody else's in the whole world.

Hughes: What about Roberto Crea, when Genentech's DNA synthesis group began to emerge? Every time he synthesized DNA for a project was his name on the paper?

Kleid: It was in the beginning, yes, especially if it was a gene that was going to get cloned and expressed. If it was a piece of DNA used as a primer or a probe, or something like that, then there's a thank you in the publication. But he didn't last too long at Genentech. Roberto left in about '82, I think.

Hughes: To found his own company?

Kleid: He went back East, founded a company called Creative Biomolecules. He has a very Italian personality, kind of volatile. He uses the word "I" probably more than most people. He and Dr. Heyneker had some personality-clash problems.

Hughes: That were occurring at that time?

Kleid: Probably from when they first knew each other, from the somatostatin days for all I know. I loved both of those guys; I just thought they were both wonderful, but they didn't think that well of each other.

Hughes: What is Heyneker doing, by the way?

Kleid: When he left Genentech he went to help start Genencor. Then he helped start another company and another one and another one. Now he's at a company called Eos. He has founded and sold about five companies. He's doing extremely well.

Hughes: What was his project at Genentech in those early days?

Kleid: Well, the first one was the insulin.[1] He helped on the insulin project, especially the yield improvement. This tryp promoter was one of his major ideas. He and Giuseppe Miozzari and I and Dan Yansura developed that. And he worked on the synthetic DNA part of growth hormone. We also made some other genes. One was called thymosin alpha-1.

Expressing Growth Hormone within *E. coli*

Hughes: What was the immediate and future significance of this semi-synthetic gene methodology? What did it mean for the company?

Kleid: It ended up being a major thing for Genentech. Instead of thinking of it as a semi-synthetic gene, I think the real concept is getting rid of the signal sequence and replacing it with a met[hionine], because now the product would be made inside the bacteria, rather than being made and secreted into the periplasmic space and then the signal clipped off. The human signal sequences are not recognized very well by *E. coli*, so they get all jammed up trying to do that process.

Cetus, as well as Rutter's company Chiron Corporation, was very interested in the signal sequence concept, as were Biogen and Gilbert. They were thinking that they wanted to secrete the product and get it out of the media and that they could run continuous cultures. So it made a conceptual difference because we made the protein inside the bacteria. They didn't know about these refractile bodies, that everything was precipitating out, so you could just lyse the *E. coli*, spin them down, and you've got your fairly pure protein right away; you're being helped tremendously. But the refractile body approach added the complication that you had to re-fold the protein, because when you make it inside the *E. coli* there are no disulfide bonds. It turns out that none of the proteins that are made inside *E. coli* have disulfide bonds because of the oxidation level.

Hughes: Was it a problem to reestablish those bonds?

Kleid: Absolutely, yes. A whole technology needed to be developed to re-fold the proteins. That was how we really started. You remember with the insulin that the A-chain and B-chain were designed to be made as chains and then the disulfide bonds recreated. And somatostatin had to be refolded . So we had some experience in the chemistry involved.

So now you come up with growth hormone, and it's all in this denatured, linear, refractile-body state. First you've got to dissolve it, get it all loosened up, because it was so precipitated that it seemed to have other *E. coli* materials with it that would inhibit proper re-folding. So it had to be completely denatured in very strong denaturing solution to get rid of all the *E. coli* stuff. Then slowly the denaturant was removed so it could re-form into its proper structure.

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[1]As Heyneker describes in an oral history in this series, as a UCSF postdoctoral fellow, he worked under a stipend from Genentech on the somatostatin project. [SSH]

That was a very different kind of process, because normally protein chemists would very gingerly break open the cell and get out the protein before it would denature. One of the major problems was that if the protein would denature they'd have to throw it away. Whereas here we were starting with the denatured protein and reactivating it, so it was typical protein chemistry backwards. In the early eighties nobody knew about that.

Hughes: You didn't publish this method?

Kleid: No, we didn't publish it. We filed patents on it in '82 or so, and then they didn't get out into the public for quite a while.[1] Eventually, the other companies started catching up because they would express their proteins, do the assays--nothing, no activity. There's one company on the East Coast that was one of the early biotech companies. I can't remember its name.

Hughes: Genex?

Kleid: Genex! Two friends of mine, including Dr. Douglas W. Fodge from SRI, went to Genex. They tried to do the same kind of thing as Genentech was doing, and they couldn't make anything work.[2] They told me that their president of research, whom they didn't like very much, said, "Has anybody really ever expressed anything?" They couldn't get anything to work. If you got a good yield it would either get chewed up by the bacteria, or it wouldn't get folded, and there wouldn't be any activity. They didn't realize the trick was to make a lot of it and to get it into these little refractile bodies. They eventually went to work on unclogging drains.[3] So it was our little trade secret that we had for quite a while.

Finally, some other companies did realize that, and one of them was Connaught Laboratories. There was a guy, Robert T. Garvin, at Connaught in Canada who gave a big talk and started writing papers. I have one of those papers where he was saying, "Here's a completely undiscovered problem for molecular biologists, totally unknown: The proteins are

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[1]U.S. Patent 4,511,502, Stuart E. Builder and John R. Ogez.

[2]See for example U.S. Patent 4,371,462, Randy I. Hecht, and compare example I with example II; U. S. Patent 4,798,791, David M. Anderson and Jeffrey C. McGuire, U.S. Patent 5,013,652, Robert L. Strausberg and Susan L. Strausberg.

[3]U. S. Patents 4,540,506, "Composition for cleaning drains clogged with deposits containing hair," and 4,610,800, "Method for unclogging drainage pipes," co-inventor: J. Leslie Glick CEO Genex "EXAMPLE 5 A clogged toilet of the washdown type in a ladies' bathroom was flushed three times without successful clearing of the obstruction. Seventy grams of Cellulase Tv Concentrate.RTM. was added to the toilet. After one hour, subsequent flushing resulted in the removal of the obstruction, resulting in normal water flow and toilet operation."

all denatured, and we found it out," and blah, blah, blah.[1] Not knowing that Genentech realized that three years before.

Hughes: Were you using that method for the expression of all those early proteins?

Kleid: Right. The early ones, insulin, growth hormone, and interferon were all fusion proteins. Interferon, which was mostly Dave's project, had methionine in place of the signal sequence. Thymosin had a methionine in place of the signal sequence, although that was a totally synthetic gene expressed as a fusion protein.

In about 1983, one of Heyneker's projects was to see if we could put the signal back on. He was able to get the human signal for growth hormone to work in another kind of bacterium, *Pseudomonas*.[2] He decided, "Well, maybe there's something wrong with *E. coli's* ability to process these signals; let's try a different bacterium and maybe that will work." Sure enough, he was able to get some secretion into the periplasm.

Then we said, "Let's look at *E. coli* signal sequences and put an *E. coli* signal sequence onto human growth hormone," and that's what we did. That eventually became Nutropin™. We had Protropin™ and then we had Nutropin™. Nutropin had the signal for ST2 toxin. Sometimes *E. coli* makes a toxin. I don't know if it's related to Montezuma's revenge. This particular signal is very efficient. So Heyneker had the idea of let's put the ST2 signal onto growth hormone. He did that and it worked perfectly.[3] The growth hormone gets secreted into the *E. coli* periplasm. You can take the *E. coli*, freeze and thaw them, break the periplasm wall, and get extremely pure growth hormone out, perfectly refolded, [requiring] none of these re-folding steps.[4] It's just beautiful.

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[1]Robert T. Garvin, "*E. coli*, as a genetic engineering host, has a serious unrecognized limitation," Battelle Bioprocess Scale-Up Symposium, December 14-15, 1983: "A serious but unrecognized limitation to the use of *E. coli* as a general host for the expression of foreign genes is that cytoplasmic proteins are synthesized and maintained in the reduced state: *E. coli* forms no disulfide bonds in the cytoplasm. ...Finally, a reflection on how this serious limitation to gene expression in *E. coli* (and perhaps procaryotes in general) has gone so long unrecognized. We believe it reflects the narrowness in training of the "new biologist" who have believed that their DNA fragment will control the activities of the host cell. Fundamentals have been neglected in the past to "clone." Careful science has been lost in the rush toward genetic engineering. ...Most of the barriers to the development of new biotechnology are front-end barriers, and the largest one is constant to the human condition: we know very little about anything."

[2]U. S. Patent 4,755,465, "Secretion of correctly processed human growth hormone in *E. coli* and Pseudomonas," Herbert L. Heyneker and Gregory L. Gray.

[3]U. S. Patent 4,963,495, "Secretion of heterologous proteins," Chung N. Chang, Gregory L. Gray, Herbert L. Heyneker and Michael W. Rey.

[4]U. S. Patent 4,680,262, "Periplasmic protein recovery," Barry R. Bochner, Kenneth C. Olson and Rong-Chang Pai.

Problems at the FDA

Kleid: Swanson decided to go forward with the Protropin™ process with the methionine and re-fold the growth hormone. We did clinical studies, and we had a hard time, as you may recall. The first time there were *E. coli* membranes and stuff in the product, which we didn't notice from our assays. The people were shot up with that and it was very painful. So we developed an assay for the polysaccharide from *E. coli* that were contaminating the *E. coli*-produced growth hormone and added a couple of purification steps and then did more clinical trials.

Hughes: In 1984 Genentech was expecting FDA approval, and yet it didn't come until 1985. Was that because of the *E. coli* contamination?

Kleid: That's right. That's because of these re-folding problems and the contamination. In fact, our mantra in 1983 was, "Four more in '84." We had one product in '83; we were going to have four more in '84. But in '83 we had this problem of first getting the membrane toxin out. Then we got it pure enough so it was good growth hormone. But then we did children, and a high percentage of them developed antibodies to growth hormone, although they weren't neutralizing antibodies. It turns out they were antibodies against denatured growth hormone. It picked up in the assay, and they didn't impact growth hormone, but the FDA didn't like those. So we went back with more purification steps. Andy Jones was the major guy at Genentech to keep purifying and purifying and purifying. In the end we wanted 99 percent purity, but it turned out we had to have 99.99 percent purity before we could get approval. It's just excruciating the number of purification steps to make Protropin™.

Hughes: Which is still true?

Kleid: Oh yes. It's incredibly hard to make. But Swanson wanted to go forward with the Protropin™ because it always looked like in another couple months we'd be fine. Then there would be a new problem and a new problem and a new problem, until October '85 was when the FDA finally gave us approval.

That had a lot to do with Jacob-Kreutzfeld disease. Earlier in '84 and '85 kids started showing up who had a very rare brain disease which was linked to growth hormone preparations coming from cadavers that had this prion virus. The pituitaries foundation decided to stop releasing growth hormone, so all of a sudden there was none available. So Genentech went to the FDA and said, "Look, our stuff is pure enough. These antibodies don't do any harm. Only about 4 to 5 percent of the kids are getting them; they're not doing anything. You've got to approve our stuff." I don't know if the FDA really did not want to do it, but eventually they relented.

At the same time the FDA was working with Lilly. They had a lot of confidence in Eli Lilly, and Eli Lilly was coming along very fast with this growth hormone project. The FDA was actively encouraging Eli Lilly to get their product out there because they didn't trust these cloners from California I think. Our product had a methionine on the front, and the FDA said, "Well, the antibodies are coming from the antigenic site caused by the methionine at the end."

We showed that's just not it. They didn't like that methionine, but they approved it anyway. But they really wanted Lilly to step in, so they encouraged Lilly to come in.

Lilly's process was to add a couple of amino acids on the front of growth hormone and then take those two off with an enzyme. Ours started with a methionine, and we just left it on. Their process had two extra amino acids, and they clipped them off with an enzyme so that they ended up with regular growth hormone. They were able to show equivalence to a product that they had been working on already, a methionine growth hormone. Their methionine growth hormone stuff was way worse than ours; it was making antibodies all over the place.

So Lilly made the met-less and said, "We did clinical trials with the met-less growth hormone and look, we're not getting antibodies anymore, so this is way better than Genentech's Protropin. You've got to approve our stuff." So the FDA said, "Okay, we're going to approve Lilly's stuff," based on clinical trails that weren't even halfway done yet. Genentech was shocked because we thought that they were way behind; we thought they were still working on met growth hormone. We had no idea the FDA was about to approve them, and then we read in the newspapers or whatever that the FDA was going to approve their product and we went crazy: Come on, this is a copy.

For Protropin™, we had what was called orphan drug status, since the product was being directed to a very small population. By working hard in developing a drug for a small population, we were given seven years of market exclusivity. The FDA said, "Fine, you can have market exclusivity for your met stuff, but we're also giving exclusivity to Lilly for its met-less." So here we had a doubly whammy. Not only did we have a major company going to compete with us, but our second-generation product, that Nutropin™ made using the ST2 signal that worked so beautifully and was much easier to make, would not be allowed on the market because now it was Lilly that had orphan drug status and seven years market exclusivity. Suddenly, we couldn't sell our new human growth hormone for seven years. So Lilly did a double whammy on us. Our best product, and the one that we really were in love with because it was so much easier to do, we were going to be prevented from marketing. Instead, we'd have to stick with our Protropin™.

In March of 1987, just before Lilly got approval, we sued the FDA because we were so mad about this change in status.[1] That suit eventually got dropped. The same day Lilly got approval, they sued Genentech to knock out all of our growth hormone patents.[2] That's when the war really started. They picked on three of our patents saying they were no good and sued us in Indianapolis to knock out our patents. That litigation lasted for seven years, covering completely the seven-year time of the orphan drug status. As soon as the orphan drug ran out Lilly said, "Oh, why don't we settle this case." Lilly ended up paying a royalty on our patents for all that time period and the case went away. But, then as I noted above, we were left with UC, and we've already talked about the UC case.

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[1]*Genentech, Inc. v. Otis R. Bowen, M.D. et. al.,* Civil Action No. 87-0605 U.S. District Court for the District of Columbia.

[2]*Eli Lilly and Co. v. Genentech, Inc.,* Civil Action IP-87-0219-C U.S. District Court, Southern District of Indiana. 5 USPQ2d 1092 (1987).

Lilly and Growth Hormone's Use in Aging

Hughes: What has this history of litigation done to your relationship with Lilly, one of your pioneering corporate relationships?

Kleid: Yes, absolutely. It went pretty far south, I would say. On a person-to-person basis they're just people, and they're doing their jobs, and some VP has an idea. From Lilly's perspective: The FDA really wants us to do this product. It's an orphan drug. We're not going to make that much money on it; it's not going to be like insulin. But there is another idea: Lilly thinks that growth hormone is going to be the cure for aging. As people get older they make less and less growth hormone. Growth hormone is believed to be one of the things that keeps us young. So they thought, you run the numbers on that and that's going to be a huge product. If everybody's going to be taking growth hormone once a month or so, shooting up with growth hormone until they die because they'll live longer, the numbers are just absolutely staggering. So they figured this product would be the entry into that market, and that market would be huge. Growth hormone has never been approved for that purpose, but it's always been a big controversy.[1]

Hughes: When did that possibility first arise?

Kleid: There was a major scientist who took growth hormone because he believed in this theory. That was back in the seventies. Of course he's dead now. [laughter] There has always been an interest in that.

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Hughes: Is Genentech interested in the application of growth hormone in aging?

Kleid: No. We have never studied that.

Genentech Shuns Unapproved Indications

Kleid: Another controversy we had with the FDA was over the concept of marketing drugs for unapproved indications. One of the unapproved indications was the use of growth hormone past puberty when there still is a need for growth hormone but in theory there is no further growth occurring. There were some questions about us promoting growth hormone for that indication. The FDA looked very negatively at Genentech for doing that. So Genentech has been extremely careful to make sure that we know every single kid that gets growth hormone, he gets

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[1]Rudman et al., "Impaired growth hormone secretion in the adult population: relation to age and adiposity," *J. Clin. Invest.* 5, 1361-9 (1981), Rudman et al. "Effects of Human Growth Hormone in men over 60 years old," *New England Journal of Medicine* 323, 1-6 (1990).

it directly from the supplier, it's all recorded. Our growth hormone is only used for pituitary problems with kids. That's it. BTG's product is sold in Mexico. You can go down there and buy all you want and use it for whatever. [Drugs for] unapproved indications, you can buy in other countries.

Hughes: I remember seeing some press coverage about use of growth hormone in children who were small for their age but weren't pituitary dwarves.[1] I can't remember all the details, but Genentech was accused of soliciting parents of short children through some school systems.

Kleid: Well, the approved indication is for growth hormone insufficiency. That definition is what controlled the market from the beginning. You can do studies on kids using growth charts, and see that they're not growing, and you give them growth hormone and it fixes that. It's not strictly the level of growth hormone. It could be the growth hormone receptors are not that active; you need a higher level of hormone in order for them to work. There is a kind of dwarf where the growth hormone receptor is broken; it doesn't work at all. Of course, that kind of person isn't amenable to growth hormone therapy. How kids are identified for need for growth hormone is if they are falling below the growth charts. Genentech has always stuck right to the line on what the indication was: growth hormone insufficiency.

Genentech's First Wholly In-house Product

Hughes: Swanson's interest was in Genentech becoming a FIPCO, a fully integrated pharmaceutical company. He wanted human growth hormone handled differently than insulin, whose development and marketing was handed over to Lilly. Could you comment?

Kleid: Sure. The insulin project we considered to be too big for us to do the manufacturing and the marketing, especially the marketing. We would be going up against a major pharmaceutical company; Lilly has first-line marketing people. We would be able to get only a small market share. As I understood it from Bob, if you were in a business you want to be the market leader, and you don't want to be the also-ran because you just get your butt kicked. We just didn't think it was really doable to do insulin.

Interferon was another product that we felt needed the power of a major company, in this case Roche, to market that product and develop the indications. Even though interferon was talked about as being a cure for cancer, how it worked and what the dosage would be and what kind of cancers it would work for and what you needed to prove to save lives was just a little bit beyond what we had contemplated in 1980 when we started on this project.

Growth hormone, on the other hand, seemed to us to be something we could tackle because the disease was well understood. What the dosage was everybody knew, and the doctors that were treating kids and prescribing growth hormone were a small number. Pediatric

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[1] See, for example: Barry Werth, "Short Kids, Tall Profits," *San Francisco Chronicle*, *This World*, June 23, 1991, pp. 10-12.

endocrinologists were a small group of people who did all the prescribing for hormone deficiencies in kids. It was a hospital-based population of doctors. With maybe fifty sales reps [representatives], we could cover the whole United States.

Marketing Growth Hormone

Kleid: I went on trips with some of our sales reps in the early days. The sales reps had a very strong interaction with pharmacists. Pharmacists were required to have continuing education meetings in their territories, and the pharmacists and the sales reps would go to these meetings. The sales reps would end up paying for the meetings and sponsoring educational presentations. I was the teacher at some of these joint meetings with sales reps and pharmacists. At some of these things I would talk about how we make growth hormone, starting from the DNA, all the way to purification. We also went to visit the pediatric endocrinologists and gave them the publications.

Hughes: All over the country?

Kleid: I just did it a few times--ones in New York and Chicago. When the sales reps first joined Genentech, I was the one who talked to them about growth hormone. In fact, I helped write a little manual about growth hormone so they would know what the heck it was and where it came from. So they invited me to go meet some of these doctors.

The reps just loved selling this product because the entire family would be involved with their child that was too short. Normally it was a boy. They weren't so concerned about the girls, but the little boy who was really short was a problem for the whole family. This product was going to be $10,000 a year, so it was major commitment. It was like a new car, or a used car at least, every year. Insurance companies would pay for that if you got all the papers signed. The sales reps would get involved with the whole program, with getting the family together, getting growth hormone prescribed by the doctor, getting the insurance coverage, getting all the details you needed, so that this [regimen] could be done without a big expense. The satisfaction you would get from this family for curing a little kid was just overwhelming. It wasn't like selling peanuts or used cars, you were developing a lifetime commitment from a family, and it was just a beautiful product to sell.

You'd go to the pediatric endocrinologist's office, and he would be loving to talk to you. He would let all the little kids stand up by the growth charts and see how these kids were doing. They would keep charts on every single kid, how they were doing each year. We did a post-marketing analysis where we measured how the kids were doing. Every single kid was enrolled, and they would get their measurements every few months. So we could chart data for the entire population. The whole program was just fantastic.

Pediatric endocrinologists have little tiny chairs lined up . So we would sit in little tiny chairs, with our suits on, waiting for the pediatric endocrinologist to come and greet us. Then we'd go into his office and share the latest data. Just everything was wonderful about that

product, although from the outside it might look like the reps were pushy or something, but from the inside it was just fantastic.

Hughes: Did you have competitors?

Kleid: Lilly was the only one. By the time Lilly got approval we were already in the market for a year or so and had established connections with all the pediatric endocrinologists. Lilly sales reps figured they could just come right in and take the market away. But because of the insurance issues and entrenchment in all of the paraphernalia that went along with getting these kids on growth hormone, the pediatric endocrinologists didn't want to bother with Lilly. Lilly wasn't going to help with the insurance stuff. It took them a year or so to figure out that they weren't going to break into the market. But gradually they did get more and more into it. Although they took some market share, they never took away the growth of the market. In other words, our sales never went down with Lilly in the picture. Sales kept increasing because more and more kids would get diagnosed as time went on because the ones that started never went off until they grew up, and that would be a ways down the road. So the market kept growing and growing and growing, so even though Lilly came into the market it did not impact our sales that much.

Hughes: There's a possibility that when you have increased knowledge among pediatric endocrinologists of a treatment that they are going to be more alert to cases of growth hormone deficiency and prescribe more treatment.. Was there something like that going on?

Kleid: Well, there was. [Because of] the knowledge of growth hormone, the use of growth hormone, by the second year the product was prevalent throughout the pediatric endocrinology community. Those people were very well-educated on the latest treatments. You can see that the numbers would increase because kids start on growth hormone and they stay on it until they grow up and even a little bit beyond; they wanted to make sure. So every year more kids would join but none would quit, so the market would naturally grow.

The definition of growth hormone insufficiency migrated a little to capture more kids that were just short. Growth hormone level goes up and down; it isn't a constant thing throughout the day. It's very difficult to show that somebody is growth hormone deficient. For growth hormone insufficiency, you look at height. Eli Lilly's people said the same thing. Today the market has flattened out because there are four companies selling growth hormone in the U.S. We've added Serono and Novo Nordisk.

There is yet another use which is with AIDS wasting. When you have AIDS, people lose a lot of weight. It turned out that growth hormone helps that, and Serono has targeted that particular area. Genentech did some studies on it but they didn't show that much. Serono did some other studies and were able to get approval in that area. BTG remains off the market, thanks to Genentech's patents, because BTG exactly copied what Genentech did. The worry with BTG is eventually they're going to come into the market and drop the price. The other companies are ethical drug companies. Ethical drug companies do not cut prices on each other. They respect each other's patents and license agreements. They don't go around crashing the price. That's what BTG wants to do; they want to become the generic manufacturer.

Hughes: What does Genentech propose to do about that?

Kleid: Well, there's not a lot we can do. Our patents are about to run out in another few years, and then it will become a generic product. Insulin has been a generic product for a long time. Novo and Lilly are the only ones selling human insulin. I don't know why generics haven't gotten into that. That's never been really protected. Other products become generic because the generic manufacturers think they can produce and sell the drug for less. Growth hormone's going to be tricky to manufacture cheaply. Any of these biotech products are going to be very tricky. BTG with TEVA will probably be the first generic manufacturer.

Hughes: How soon is that likely to happen?

Kleid: I'd say probably in the next couple of years. Our patent was just upheld. We've had this patent battle with them almost as long as with Lilly.

Aiming to Become a FIPCO

Hughes: Did Genentech's success with growth hormone success prove to be what Swanson hoped, namely indicating to the world that Genentech could cover the whole range of drug production, that it wasn't just an R&D firm?

Kleid: I would agree with that, but I don't know if he would. It was the mantra from the get-go that we were going to be a fully integrated pharmaceutical company. We were going to have the whole thing: manufacturing, sales, and everything. And we were going to do it by 1983. Now, October '85 we got our first drug, growth hormone, approved. It was like a sigh of relief, "Okay, we finally are able to do this." The manufacturing of growth hormone was way more difficult than we thought it was going to be. Sales turned out to be way easier. We really did a great job on the sales. We saturated the market pretty much right from the get-go. So yes, growth hormone did prove that we could be a fully integrated company, but it didn't meet our expectations because it came too late. And then immediately we had this competitor, Eli Lilly, which didn't make us feel like we made it.

Genentech's Interaction with KabiGen

Hughes: How much interaction was there with KabiGen? Did Kabi send people to Genentech?

Kleid: Yes, in the beginning. Maureen McKelvey wrote quite a bit about that.[1] Kabi brought some protein chemists to Genentech. The idea was that they would apply the purification scheme from pituitary to the growth hormone out of *E. coli*, and they actually did that. There was the early *E. coli* that we made without the tryp promoter, which made a small amount of growth

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[1]Maureen McKelvey, *Evolutionary Innovations: The Business of Biotechnology*, Oxford: Oxford University Press, 1996.

hormone that was soluble, that didn't go into the refractile bodies. So they lysed the *E. coli* and they went with the old-time Kabi purification scheme. That was useless because the yield was so low and you were throwing away 90 percent. So we had to develop a process from scratch with the re-folding step. I described how Andy Jones did it. It was a huge project and every time the growth hormone needed to be more and more and more pure.

The amount of information from Kabi from their previous experience was not that valuable in the end. But together we did face this problem of purification. My understanding is that it was so difficult that Kabi people went in their direction and we went in our direction and eventually developed processes that we were happy with. Genentech went forward with Protropin™. Kabi started with--I forget what they called the stuff--the met growth hormone. Then the Heyneker process with the ST2 signal sequence was completely finished at Genentech, ready to go. We were prohibited from getting approval. But Kabi took that process and sold Genotropin™--they put our name on it. (Later we called the same material Nutropin™.) They weren't under the Orphan Drug Act, so they were able to market our second process, which was <u>completely</u> developed at Genentech and handed over to them at the end stage so they could just run with it. That process was so much easier and was so much nicer. They benefitted more than we did.

The Pharmacia-Upjohn vs. Genentech Case

Kleid: Kabi eventually got bought by Pharmacia,, and Pharmacia eventually merged or was bought by Upjohn, and became Pharmacia-Upjohn. Our contract with Kabi was for twenty years, so that would end in 2000. The contract that Kiley wrote has a funny phrase in it. It said, since there were no patents in 1980, "We're going to give you the bug. As long as you use the bug for growth hormone you can do that, free of Genentech patents. After twenty years the bug's yours." They read that agreement to say that after twenty years they owned title to the bug that makes growth hormone and Genentech didn't anymore. They sued us and it went to arbitration and we had a hearing on it. We still haven't gotten the answer.[1] We put in a case this last year where we said, "The agreement doesn't say that you take title and we don't use our bugs anymore. The agreement says that you are free to use it whenever you want after twenty years." Pharmacia-Upjohn had a secondary argument that they taught us how to make growth hormone--we didn't know what we were doing, and they contributed hundreds of pieces of information, and they listed them all. In the end it turned out to be one or two tiny little things they may have contributed.[2]

Hughes: Why is this case arising now, after years of relationship?

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[1]The case was finally decided in the summer of 2002 in favor of Genentech.

[2]None of Pharmacia-Upjohn's claims were successful.

Kleid: Well, it's not Kabi anymore. There are new VPs, they have new bottom lines, and they said, "We can get all of the growth hormone market from Genentech if we can just convince the court that we own the bug and Genentech doesn't anymore."

Hughes: I gathered that the relationship was quite close and personal with some of the early people at Kabi. You mentioned Åberg who, by the way, I learned from reading McKelvey, went off to form KabiGen. Do you have any comment to make about that company? It's one of the first biotech companies.

Kleid: I wasn't privy to organization changes at Kabi and KabiGen. Kabi had a lot of government sponsorship and KabiGen was more venture type. I don't know the ins and outs of how their agreements were structured.

One of the main scientists at Kabi was Linda Fryklund, who was a protein chemist and studied hormones. I don't know how much interaction she had with Genentech; I think extremely little. But in this recent case she resurfaced as one of the main protagonists, explaining that Kabi taught us what to do rather than the reverse.

It's motivations of individuals at the top. You've got to look at this Pharmacia-Upjohn and try to imagine what a VP would read [into] this contract and say, "Let's get Genentech out of the growth hormone business because this contract says that we own the bug." And then that VP would mobilizes all these lawyers to come attack Genentech and make us defend ourselves. These guys are nuts.[1]

Companies have a kind of life of their own. They're kind of like organisms that fight with each other all the time. The "corporation" organism as a whole is not a human and has no conscience. The CEOs have to keep their VPs under control. The VPs are trying to make as much money as they can for their company and get themselves promoted. But, from the top down there has to be a message that says this kind of activity needs to be reasonable, not excessive and certainly not illegal or else everybody is going to get in trouble. Do your best, but do it right. I think Genentech's always been in the right because we are trying to do what's best not only for Genentech's employees but also for our customers.

Hughes: It's supposed to be an advantage to a company, particularly in a new area of technology, to be a first mover. But you could also argue that pioneering companies get a lot of flak because they're doing it first; their patents are often the initial patents; anybody who comes along next is a competitor.

Kleid: What the innovator gets is a knife in the back from the copycat. [chuckles]

Hughes: Have we covered growth hormone to your satisfaction?

Kleid: Maybe. [laughter] You can see that it is one incredible story. The growth hormone legal battles are not over yet. BTG's appeal finally was decided last week and they lost. Now BTG says they're going to use a different way of making growth hormone. Instead of Genentech's

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[1]Since the arbitration was under European rules, the loser pays the legal expenses of the winner. Genentech expects to get all of its legal expenses back.

method, they are going to use Novo's method. Believe it or not, they're in a suit with Novo now on the method that they're trying to use that's patented by Novo. So it's not done yet.

Biosafety at Genentech

[Interview 4: January 8, 2002] ##

Foundation of a Committee and Rationale

Hughes: I read that in the very early days you were the appointed biosafety director. Did that happen very quickly after you arrived?

Kleid: Yes. Not only biosafety but radiation safety. Since there were only two scientists here, and one of them wanted to work in the lab, then somebody had to do the other jobs. So I got saddled with all the extraneous things that we needed to do in order to be able to do the experiments.

In order to clone in our laboratories we had to have a biosafety committee if we were going to follow the NIH guidelines. I had set up a biosafety committee at SRI so I knew the procedure. You needed to get some people, fill out some papers, and send it to the NIH Recombinant DNA Advisory Committee. I think we did all of those things and established a biosafety committee. The same thing with radiation. In the State of California, if you use ^{32}P or any other radioisotopes, you needed to have a license. So there you also needed a little safety committee, so I got stuck setting that up too.

Hughes: The NIH guidelines applied only to institutions receiving federal money, which Genentech was not. Is that not true?

Kleid: Right, we didn't.

Hughes: So why did Genentech think it was necessary to comply with the guidelines?

Kleid: You could voluntarily comply, so we chose to voluntarily comply.

Hughes: Was there a political dimension to that decision?

Kleid: I don't think so. It wasn't that big of a job to comply. I think the guidelines in general were a protection thing: If you follow the guidelines people aren't going to get worried that you're going to make something that's going to get out of the lab and terrorize the neighborhood; you're being responsible. We wanted to be responsible. Maybe it was basically political, because there was no hazard, and we didn't have to comply. But I think it was a prudent thing to do, and it wasn't that difficult.

Hughes: In 1978, when you arrived at Genentech, the recombinant DNA controversy was raging. It would not have been politic for Genentech to be known as a company that did not follow the guidelines. I'm surmising that the public image of the company would be improved by

following the guidelines. But the way you're making it sound, following the guidelines wasn't a big deal.

Kleid: That's right, it wasn't a big deal, and it wouldn't have been a deal at all if synthetic DNA had not been covered in the guidelines. The issue was cloning something that you didn't know what it was. Here [with DNA synthesis] we knew exactly; we made it. From what I understand, Paul Berg had something to do with adding synthetic DNA to the guidelines. There really was no reason to have synthetic DNA under the guidelines because all the concerns were about accidentally cloning a piece of an unknown gene. Synthetic DNA is just a chemical that you were going to make lots of copies of. So it was a shame that synthetic DNA was added because it did make us do this committee.

The Gilbert and Rutter teams did cloning abroad to escape the guidelines because they were working with cDNA that required very high containment conditions to carry out the work. The thought was that they might clone something that they did not intend to clone. Genentech did not have to clone insulin-encoding DNA abroad because we were working with synthetic DNA. Under the guidelines, these types of studies only required good laboratory practice. But, you still were doing recombinant DNA research, and that kind of work fell under the guidelines, so we still needed a biosafety committee to confirm that we were doing things right.

Hughes: Do you remember when synthetic DNA came under the guidelines?

Kleid: I think it was in the guidelines that came out of Asilomar.

Hughes: The first set of guidelines were announced in June of 1976.

Kleid: [pause] I think it ended up in the original guidelines, though I'm not sure about that. You might want to check and see if there was a later version in '78 or something.

Hughes: There were several revisions. The momentum over time was to loosen the guidelines. How long were you safety director?

Kleid: Well, I think until about '82 or so.

Procedure

Hughes: And what did you actually do?

Kleid: Well, every time we had a project that involved cloning of DNA or cDNA, we had a proposal from one of the scientists submitted to our biosafety committee. One of the scientists would write down what the project was about, what the starting materials were going to be, and that he was going to follow the guidelines.

Hughes: And that was sent in to RAC?

Kleid: No, it was sent into our own biosafety committee. And our biosafety committee then would have a meeting every four months or so. We would invite the members of the biosafety committee to look at the project and approve it. Then it would go into the Genentech files. There weren't very many things that needed NIH approval by the NIH Recombinant DNA Advisory Committee (or RAC), but every once in a while there was. We would go to Washington, D.C. and tell them we were going to do project X or Y.

Hughes: And the internal review was serious? It wasn't a rubber-stamp approval?

Kleid: An outside consultant from the Naval Research Labs across the bay would review the project before giving his approval. I was on the committee. The guidelines said that there should also be on these local committees an ordinary non-scientist, and that could be an employee from our organization. We also had a vice president of the company on the committee. Bob Swanson himself would sign off on these approvals. I don't know if he went to all the meetings, but everything was reviewed extensively.

Hughes: So it was a serious enterprise?

Kleid: Oh yes, it took some time to do.

Request to Exceed RAC's Ten-liter Microbial Culture Limit

Kleid: We had a couple of projects that made it to the NIH RAC. One was making the insulin A- and B-chains at greater than ten liters. That was a step that required the approval of the Recombinant DNA Advisory Committee at the NIH. We sent in that proposal, and I remember that it took a while for them to respond. They said, "Well, we don't have any mechanism for approving this non-government funded work at the present time." This was 1979, I believe. So we sent them a letter saying, "You either consider our approval request, or we're going to go ahead and do it." And they didn't write back, and they didn't write back. So we sent them a letter saying, "Okay, we're doing it. We're starting." And we did make a few runs with higher than ten-liter cultures. Then we got a letter back saying, "Wait a second you guys, we will consider your request after all. You need to get this approved."

Hughes: So you had to stop the fermentation?

Kleid: We stopped it, and then we went back there. We forced them to get the approval process for scale-up organized. As you said, since we didn't get NIH funds we didn't need to do this; we were following the guidelines voluntarily, and then RAC needed to do their part voluntarily.

Hughes: The guidelines initially were largely set up for academic labs which would not routinely be using ten-liter batches. This ten-liter limitation was one of the things that had to change when recombinant DNA became an industrial process, right?

Kleid: Oh, absolutely. But even in academic labs there was fermentation being studied at greater than ten liters. And again, [Genentech's insulin] project used synthetic DNA fragments. It was a

synthetic A-chain gene, a synthetic B-chain gene, grown in two different organisms, and we needed to scale this up--ten liters was too small to really make a good prep. So the safety was nothing to worry about, but the RAC approval process wasn't quite ready to go. Did you find any articles about Genentech not following the guidelines because we went ahead and did this?

Hughes: No.[1]

Kleid: It did make the papers.

Hughes: Genentech wasn't the only one to make the papers because of a supposed violation of the guidelines.

Kleid: That was really kind of unfair, because RAC knew everything about the insulin project.

Hughes: Were you forced to use the weakened K12 line of *E. coli*?

Kleid: Yes, we did that.

Hughes: Did that cause any problems?

Kleid: We needed to get that changed for scale-up because the original *E. coli*-approved recombinant DNA research was [for] a particular strain that was very easy to transform, to put plasmid DNA into. It wasn't particularly good for high-density fermentation. It didn't like to go to high density. We wanted to change to a healthier *E. coli* K12 organism. All the strains of interest were *E. coli* K12, but there was an NIH-approved one that was even more mutated, and we wanted to get away from that, and maybe even try *E. coli* B to see how that one would work in fermentation.

Hughes: And did you?

Kleid: We eventually did, but we got approval for these things.

Hughes: The RAC process was holding you up? You had to stop things occasionally because they hadn't been approved?

Kleid: In a sense, yes. There was a process we had to go through, but I don't know if you can say that RAC caused us to go slower; we just did more work in other areas. We were allowed the ten-liter fermentation, and we would run the ten-liter fermenter over and over and over again. In the end, you would have a bigger batch than ten liters, but you never grew it over ten liters at one time. We had a seventy- or eighty-liter fermenter right next to the ten-liter, so we could have done eight batches at once instead of running eight ten-liter batches one at a time. It just took a bit more time.

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[1]Prompted by Dr. Kleid's question, I later found: "Insulin Research Raises Debate on DNA Guidelines," *New York Times*, June 29, 1979, p. A18. There doubtless was additional coverage. [SSH]

Hughes: Anything more to say about Genentech's biosafety, radiation protection committees as time went on?

Kleid: I think they eventually got a lot easier. One project that we got RAC approval for was for cloning of the hoof-and-mouth disease virus. That was a big project, getting that approved. In general, I think it just was unfortunate that the guidelines covered the replication of synthetic DNA using recombinant DNA technology.

Hughes: There weren't many people using synthetic DNA.

Kleid: There was virtually none. There were a couple of projects here and there. So I think that particular addition to the guidelines was directed at Herb Boyer's project.

Dan Adams and Biogen

Hughes: I read that Inco--the International Nickel Company--had a very early association with Genentech, probably before you arrived on the scene.

Kleid: I can tell you what I know about it. A guy at Inco named Dan Adams was in the venture-capital area and knew Bob Swanson. Inco was one of the early investors in Genentech. They made a fairly minor investment, although in those days it might have seemed like a lot of money to you and me. Dan Adams was very impressed with the way the company was structured--taking advantage of science published from the universities and founding a company, getting money from corporations, and all that sort of stuff. So Dan Adams decided to start another biotech company based on Genentech's model, and that company was Biogen. Bob wasn't so happy with Dan Adams for taking Bob's company plan and starting another company based on it. So Dan Adams gave Genentech some interest in Biogen. Genentech got some of the original shares of Biogen because our corporate plan was used as a model for Biogen's plan. Bob went to one of the first board meetings at Biogen. I'm not sure what country it was, but he went to the meeting. It kind of made a brouhaha, because they didn't want Bob there. So he ended up selling our shares of Biogen back to Biogen and putting some money on our books. Bob liked to explain--that was our first profitable sale.

Diamond v. Chakrabarty

Hughes: In 1980, the Supreme Court came to a decision in *Diamond v. Chakrabarty* that "life forms" could be considered for patenting. Were you and others at Genentech following that case, thinking that the decision could impact the future of commercial biotechnology?

Kleid: Well, yes, we were following it. I had some interest ever since learning about it from Tom Kiley who was our patent attorney--and whom I had gotten to know at that time. All of Genentech's patent applications, when they got to the [U.S.] patent office, were put aside and

not examined, pending the outcome of the Supreme Court decision on whether you could patent life forms.

[Ananda] Chakrabarty made microbes by mutating them so that they would eat oil. The idea was to clean up oil spills. He tried to patent those things, and the patent office said, "These are life forms; they're not patentable." So General Electric appealed that case, and a lower court found against Chakrabarty, so he had to keep appealing. He appealed all the way to the Supreme Court. I think that patent office had something to do with making sure that the case got to the Supreme Court. The Supreme Court said that since the microbe was made by the hands of man and it had a use, it fit within the scope of the patent laws and there was no reason why you shouldn't be able to patent it.

Prior to getting the Supreme Court's decision, Genentech was worried that they would extend that decision to plasmids and DNA molecules since they are theoretically alive because they have their own origin and replication. Were they going to be swept into this decision? And the question was, were we going to be able to have any patents at all? That would have been devastating, because then everything that Genentech worked on would end up being generic immediately. As soon as we did something valuable, everybody would just copy it.

Hughes: That might have killed the industry.

Kleid: Well, yes. It would have certainly killed us, and we were the industry. [laughter] So Tom Kiley wrote an *amicus curiae* brief to the Supreme Court. I don't know if the justices mentioned his brief in the decision, but it was very well reasoned, and the Supreme Court came out just exactly as we had hoped.

Hughes: There were a number of briefs. All of them argued for the right to patent life, with one exception filed by an organization represented by Jeremy Rifkin.

Kleid: I think the way you frame it--patenting life--is the way Rifkin portrayed it. But you're not patenting life; you're patenting something that you made that just happens to be able to replicate itself.

Ethical Issues in Recombinant Science

Kleid: Most of Rifkin's interest has been with the Evangelicals, and they are able to raise a lot of money by scaring people. They are anti-science; they're afraid that scientists are doing things that God did not intend human beings to do. So they want to stop these horrible scientists. It really is Evangelicals against science. Genetic engineering was a nice fruitful example for them to raise because you could get a lot of people fired up about scientists doing horrible things in that particular context--gene splicing, cloning humans, etc. If it wasn't us under attack, it would be somebody else. Although Rifkin claims that he's trying to stop the biotechnology industry from going wild, he's really just trying to raise money for his own account.

Hughes: Circa 1975, 1976, and somewhat later, there were prominent scientists speaking out about the potential danger of recombinant DNA, including George Wald and Robert Sinsheimer.

Kleid: They were still talking about the unknowns: Maybe there was something about nature that we are tampering with that could go out of control, that if there was the ability to do these kinds of things [genetic engineering] then God should have been doing it all along. When you think about it, God gave us the power to read our own genes. No other species on earth has been given the power to read their own genes. Of course, He also gave us free will so people can do bad with this power. So it depends on society to make the laws and say, "You're not going to do this, and you can do that." As scientists we fully participate in the legal system and our whole system of what is right and wrong.

Evangelicals will say, "Scientists don't believe in God." That's crazy. Anybody who has looked at these genes and seen how <u>incredible</u> they are and what happens at the genetic level could not say, "All of this was put together by happenstance and luck." It's impossible to believe that. I'm sure that most scientists believe in a greater force out there, defined however they want. But certainly just because you cut and paste DNA doesn't mean you're going against God, or don't believe in God, or that you are "playing God." You're not. Scientists are just gathering data and trying to make useful things.

Hughes: It's interesting how these ethical issues persist. They're embedded in the current stem cell and human cloning debates.

Kleid: It's the same people. Rifkin is still here talking about the same exact things. I think there are some points to be made about creating human beings. Kids are very expensive to raise. Who's going to want to do that anyway? It's still the same people, the same Rifkins, the same Evangelicals are still trying to raise money for their same causes. They set themselves apart as being holier than the rest of us, but it's just not the case.

Hughes: Do you have a philosophy about how science as a discipline should respond in these cases?

Kleid: I'd agree with the way scientists have been doing it, which is that there are basically no secrets. Everything is published; you can read about all the work. Scientists are not in some hidden ivory tower on some island, doing crazy experiments, like you see in the movies. They're in academic institutions or in companies. Although the companies have some proprietary things, they still publish everything, and everything goes to the FDA. So it's all for everybody to see.

Whether people understand it or not is a little tricky. Scientists have tried to explain what they're doing so that the public is comforted, but that has a tendency to backfire. Scientist don't explain it right, or they end up making people more scared, with the help of the Evangelicals. It's always a difficult balance. Importantly however, everything is open: Always tell the truth, and the truth will win out. Scientists are trying to discover what nature is all about, like an asymptote approaching the truth as written by Mother Nature and God and whatever else is out there. What can possibly be wrong with that?

Hughes: [pause] All right.

Kleid: [laughing] So much for my thoughts.

University of California v. Hoffmann-La Roche, 1980

Hughes: Another thing that was going on in the early 1980s was a UC lawsuit in which Genentech was a party in which a human cell line producing interferon was transferred from one institution to another. I remember Bob Gallo was involved.

Kleid: There was another, David Golde.

Hughes: Golde apparently was the originator of the cell line. He passed it to Gallo, and Gallo passed it to the Roche Institute of Molecular Biology, which passed it to Genentech.

Kleid: Genentech, even now, doesn't get samples directly from people to do research on. It just hasn't happened that much. But this particular cell line was very valuable in and of itself, and the person from whom the cell line was originally taken wanted a piece of the funds that it might generate. But a cell line is just a research tool. I think in the end the case turned on the fact that the person gave the sample to the university to do with what they wanted and really had no claim on it because it had absolutely no value to that person. But it did have some research implications. I think the case was in the courts for quite a while, but in the end it was really superfluous. I don't think we ever worried about it at all. There were other cell lines that were very valuable to Genentech; the tPA project had a cell line from a particular individual but nobody ever made a claim on it.

Intellectual Property at Genentech

Patents Rather Than Trade Secrets

Hughes: Was it understood from the beginning that intellectual property was going to be at the core of this new field?

Kleid: Well, the scientists and Bob Swanson and Boyer made a deal right at the beginning.

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Kleid: The scientists wanted to publish their work and to be part of the academic community. Bob saw danger in that. Number one is that everybody would just copy Genentech inventions. So he said, "Well, if our scientist publish, then they have to help us with the patents." He told each of us: "You have to agree that before you submit the paper that we get a chance to write a patent on it and protect our work in that way. So our company won't rely on trade secrets." The other choice was you don't publish and we don't patent and we just keep it all a trade secret. We, the Genentech scientists, didn't want to be part of an organization that was going to be all trade secrets, because we would disappear and be so-to-speak "total pawns of the industry" in a way.

Instead, we wanted an organization that was totally open and totally part of the academic community. So we had to make this deal.

Hughes: Who's we?

Kleid: The original group of scientists, which included Dave and Herb Heyneker and Herb Boyer and Art Riggs and me, the group which was going to publish. We could protect our inventions with patents. Although none of us had had any experience with patents. Throughout our university training, our Ph.D. training, not a breath about patents.

Hughes: Not even at SRI?

Kleid: We patented at SRI, and they had a staff for patenting and licensing, not unlike the Genentech situation. I assumed that nothing I did would be patentable. At Genentech, we had no scientists in molecular biology, as far as I know, who had any experience in patenting anything at all. So we learned from Tom Kiley, who actually at that time didn't have that much experience either, although he had been a patent examiner in the U.S. Patent Office, and then became an attorney, and then came to Lyon and Lyon. He drafted some of his very first patents for Genentech.

So we said we will protect our inventions by patenting because otherwise everything we do is going to be copied by some major pharmaceutical company. We thought they could copy it rather easily, and maybe they would even beat us to the final product at the end. Our plan was that we were going to publish the cloning of these genes, synthetic or cDNA. Then four or five years down the road we would maybe have a clinical trial. It would take six or eight years, if we were lucky, before the drug would be approved. In the meantime, somebody could be copying the whole time, and they might even beat us even if we kept these things as trade secrets. So the only way was to patent.

We made the assumption that the major pharmaceutical companies would respect our patents, and they wouldn't just rush in and copy everything. For the most part, we were right. But what we probably didn't expect was that they immediately filed lawsuits against us, that our patents were too broad and covered too much. As soon as Genentech started making money off of its inventions, it was like a feeding frenzy for attorneys to see if they could knock out the patents or copy them or whatever. From the time the money started coming in, we've been in patent litigation.

Early Genentech Patents

Hughes: What was the first Genentech patent to issue?

Kleid: The first one of any substance was one of the Riggs patents.

Hughes: Riggs-Itakura?

Kleid: Riggs-Itakura actually took a little while to issue.

Hughes: Yes, it seems to me that didn't issue until 1987.

Kleid: Yes, but it was already an issue in Europe. The growth hormone patent about the semi-synthetic gene concept was one of the earlier ones to issue. That one got through the patent office rather early.

Hughes: Why the difference in issue rates?

Kleid: It has to do with the breath of the claims. If you want a narrow claim, patent examiners will usually buy off on that. But if you want something really broad, they keep coming up with more and more reasons why the claim is not good, so there is more bickering and going back and forth.

Hughes: The Riggs-Itakura patent grew out of the somatostatin work, did it not, but was not narrowed to just the somatostatin research?

Kleid: Let me explain that, because you're exactly right. The claim was to using a bacterial promoter to make a non-bacterial product. We cut out the gene for β-galactocidase, for example, and put in the gene for growth hormone. So now the bacterium was thinking it was making β-galactocidase when instead it was making growth hormone. So the patent described and claimed putting the promoter juxtaposed next to your foreign gene in a plasmid so that it would get expressed. This plasmid was eventually called an "expression vector." Now that's pretty darn broad; that covers everybody. It was different because prior to that people were putting the entire gene into bacteria, whether it was in yeast or whatever. They were taking the genes and putting them in the cells and seeing if you got any protein product expressed. But, as it turned out, you didn't make anything because the promoters were different.

So this Riggs-Itakura concept not only solved that problem but also made it possible to make more and higher quantity protein because now you were optimizing. The bacteria loved this promoter, so they were going to do whatever they could to make as much stuff as you wanted. So that concept was new, and the DNA to make it was new, and the whole process was new, so that was a kind of a basic concept patent.

Hughes: So everybody in the field had to license the Riggs-Itakura patent?

Kleid: Exactly.

Hughes: And the breadth of it, to reiterate, was what slowed down the issuance of the patent?.

Kleid: It had an impact on getting the patent issued. The patent examiner said, "Wait, all you're doing is putting a bacterial promoter next to a human gene. What's the big deal to that?" So it took a while to convince the patent office that the expression vector concept was a new thing and that there wasn't any prior art.

The Cohen-Boyer Patents

Hughes: Tom Kiley called the Riggs-Itakura patent the "industrial corollary" to the Cohen-Boyer patents.

Kleid: Sure, right. Although, if the Cohen-Boyer patent was done in industry that would have been-- [laughs].

Hughes: What would have happened?

Kleid: Stanford and UC shared a lot of royalties on the Boyer-Cohen patent, which was basically about making plasmids. While the Boyer-Cohen patent was pending, the attorney took some paragraphs out of the somatostatin paper and put them into the Cohen-Boyer patent and tried to claim our expression vector invention as well.

Hughes: What happened?

Kleid: He never got claims to the expression vector where you have a vector designed to transcribe and translate your gene. So the expression vector concept was the next stage. Now the Cohen-Boyer patent was licensed to everybody for fees rather than tied to product sales. For seventeen years the two universities collected these fees and did pretty well with that.

Hughes: What's the significance? Does that mean more income because even if you don't end up with a product you have to pay the license fee?

Kleid: Right. Patents are licensed either exclusively or nonexclusively in the making, using, or selling of some product. So you need to practice this patent to make this product. Then the product is sold, and then you get some royalty on sales. But this industry was quite a way away from a lot of sales, so they figured they could make more money by licensing year-to-year to companies using this technology. So if you wanted to make plasmids in your company, you had to send a check to Stanford each year.

Hughes: There was a fee tied to products as well. There was the licensing fee and then there was another fee if and when you got a product.

Kleid: Yes, I think you're right. There was, but it wasn't terribly expensive.

Hughes: I know from having talked with Niels Reimers[1]--

Kleid: The designer of this licensing strategy.

Hughes: ---that somewhat because of the political situation at the time the idea was to make the technology readily available and not to exclude companies because of high fees and particularly not to incite litigation..

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[1]See the oral history with Reimers in this series: http://bancroft.berkeley.edu/Biotech/archive/. [SSH--note that address is case sensitive]

Kleid: It's a balance: When the payment gets so expensive it might be cheaper to knock out the patent using the courts. Because Stanford could say, "You're not licensing this. Where are our funds?" Their only remedy was to sue that person. So they knew the line was where people were going to balk. I think that was the wisest thing to do--for all the reasons Niels expressed to you.

Genentech's Patent Portfolio

Hughes: Swanson said at a Hambrecht and Quist conference in 1985 that by that time Genentech had 117 issued patents and almost 2000 applications pending worldwide. How does that compare to other companies in the field and also to other high-tech companies?

Kleid: It was right up there. For a company our size, we were certainly up there at the very top. IBM files thousands and thousands of patents, but that's a huge company, and their patents are on the tiniest little nudges of improvement. They supported the budget I guess by filing so many patents. Whereas other companies--I think Xerox was one of them--filed really broad claims. Compared to other companies in our industry, we were by far the leader, and we were above most universities. Right now, Genentech's patent portfolio is by far better than any other in our industry.

Hughes: Better in what way?

Kleid: It is a portfolio that protects our products and has breadth to it so that we get royalties from a lot of other people. We get royalties from Immunex for sales of its very popular product for arthritis, and we get royalties for factor 8, and we get royalties for hepatitis vaccine. A lot of products that we don't make, our initial inventions made those products possible. We have a tremendous patent portfolio.

Hughes: Is some of that due to the first-mover effect, the fact that Genentech was first in the field?

Kleid: That's one of the things about getting an invention, you have to be the first to do it. Then you have to have people to draft the patent as quickly as possible, and then people to prosecute the patent and get claims that not only cover your product but cover your product broadly enough so that it can't be knocked off by somebody else.

Hughes: So you had good intellectual property attorneys?

Kleid: Exactly. Some of the leaders in the field.

Hughes: Does Genentech have a reputation for being aggressive in terms of intellectual property?

Kleid: I wouldn't say that. I would say our portfolio is aggressive. We have claims that are as broad as we can get. But what we do with our patent portfolio wouldn't be what I would call aggressive where you go out there and torture the landscape. We really have not enforced our patents against anybody except people that are exactly in our business. We've had a lot of patent battles on growth hormone. Lilly has no trouble with others that wanted to copy our human insulin product; we've never had an insulin case. tPA created a lot of patent battles, again

because other companies wanted to make tPA. We've filed a suit against Amgen, which I believe is going to be heard--the decision is pending at the Federal Circuit--on their hormone for white blood cells.

Hughes: Neupogen.

Kleid: Neupogen, yes. Amgen's process infringes one of our process patents. That is the only case I can think of where we enforced our patent against a company which was making a product that Genentech was not making. Everybody else, we could make a deal. You can go to a company and say, "Look, I know your product infringes our patent or uses a process of ours. Why don't you pay us a royalty? We're not going to shut you down; we're not going to demand usury fees. Just pay what it's worth. We made a contribution to your product." That usually is how everything works. Then everything follows from there.

The other thing is, we use our patents when we license out a product that we developed at Genentech, for example, Factor VIII for Bayer, or hepatitis vaccine for Smith Kline, or interferon for Roche. The company licenses our patent to make and sell that product. Then we get our license fees (or royalties) on the sale of the product that we put them in business with. So in that way, it's critical to do the research and take care with the intellectual property. Genentech can't make all the products, so we license the patent that claims a method to make interferon to Roche, and Roche makes the interferon. We also license the patent to make Genentech products in other countries. For example, we licensed European companies to make and sell tPA outside the U.S. As long as our patent is alive and in force, they'll be paying us royalties. That's not "aggressive" either, I would say. But the majority of the products now for sale from the biotech industry came out of Genentech science, and we get royalties on almost everything. So it looks pretty aggressive.

Hughes: Was the royalty stream in the early years of Genentech a major source of income?

Kleid: In the earliest days, the income came from these benchmarks. But once the product got on the market, then the royalties came from product sales. They made a difference in the late eighties. But we were supposed to have our own products by then. Royalties were quite important in the late eighties because they paid for a lot of salaries here. The royalties on tPA and insulin and interferon, especially on interferon, weren't as high as we hoped, but they did make a difference to the bottom line.

Patenting and Its Parameters

Hughes: Please comment on the effect of patenting on the flow of information in science.

Kleid: I think it has had a positive impact on it. The whole idea of a patent is you tell people how you did it in exchange for seventeen years of exclusivity. So you are disclosing the invention to the public in exchange for being given the patent rights. The idea from Thomas Jefferson's time was: You tell me how you did it, and I'll let you practice your invention exclusively for a limited period of time. I'll let you have the right to exclude others. Actually, all a patent does is give you the right to exclude others from using your invention for that time period. But others

can use it in research, and they can use it any other way. They just can't use it to make products, to sell things unless you let them with some kind of agreement.

What usually happens at Genentech is the scientist wants to publish his paper, or he wants to go to a meeting and talk about his project. So before he does that, he's got to go to the patent attorneys and see if there's anything patentable there. If there is, then they've got to write up a patent [application] for it before he sends in his paper. So there is a trade-off between those two things, and actually this [policy] caused all of Genentech's major discoveries to be published and have patent applications filed very quickly after the work was done.

Part of the advantage in the patent system is the first one to file for a patent has a big advantage, because for the second guy your patent is prior art to his. So you want to be the first. The only caveat is that in the U.S. the person who deserves the patent is the first one to invent, not the first one to file a patent application. If you filed your patent application second, you can sometimes prove to the U.S. Patent Office that your inventor actually thought of it before and was working on it and just filed the patent application a little later. That's one of the areas of litigation that I've been involved in since I came to the legal department.

Genentech Refocuses on Human Pharmaceuticals

Animal Health and Genencor

Hughes: [pause] By the early 1980s, Genentech was applying recombinant DNA technology in a variety of fields--industrial chemicals, agriculture, food processing. Or at least that was what it was advertising. Why, within a few years, had it pulled back into being essentially a drug company?

Kleid: I think the answer lies in the value of the product on a per-unit basis. We had a big effort in animal health, for example. But it turns out that animal drugs are sold at just tiny margins over the cost of manufacture. Whereas when you get into human health care, you're talking about here's a cure for a disease that's going to kill somebody. Most of the Genentech products are that way. This [drug] is lifesaving; the product is meeting an unmet medical need. The delta between what it costs us to make the stuff and sell it is considerable. We just could make more money and pay for more salaries by chasing down drug products. In agriculture, if you could invent a new type of corn then you could-- There's a lot of corn out there, and it's sold for a huge amount of money, but clearly what you're selling is the seeds. The amount of money you can make on those seeds was not something that Genentech could get its hands around.

So we spun off those kinds of companies. We started companies that were in that area. One of them was a collaboration between Genentech and Corning Glass, which became Genencor. That company emphasized industrial enzymes. There were about a half-a-dozen enzymes that were used in products, and Genencor thought that they could improve on those enzymes and maybe make them a different way. Those products had a bit of a delta that was worth going after. Genencor consolidated with several other companies. It's a major company these days but it took quite a while for it to be profitable.

Hughes: It has no association with Genentech any longer?

Kleid: We eventually sold our interest in that company. It got bought several times, in fact. The amount of investment that it takes to bring those products along is still a lot. Then at the end of the day you get a product that just doesn't have a sufficient delta.

Hughes: So the biggest delta--if that's the term--is with drugs for human use?

Kleid: Drugs for human use. And specifically for unmet medical needs, where you have a cure for a disease out there without a competitor. We haven't been interested in making the next aspirin.

Hughes: There was some fanfare about this broad-spectrum approach that Genentech was going to launch. I read a press release of 1981 announcing the arrival of Ray Gomez from MIT who was to head a new department of industrial microbiology.

Kleid: Exactly.

Hughes: Did that department eventually become Genencor?

Kleid: Yes. It was just too much for us to chew on. Also, I think the board of directors may have had an impact on this too. They felt that Genentech had a couple of <u>very</u> important things on its plate--growth hormone, tPA, gamma interferon. These things appeared to be going too slowly, and the FDA approval process was very difficult. It was important that Genentech focus its efforts more. The people working on these industrial enzymes had nothing to do with the Genentech scientists that were testing our drugs and trying to get FDA approval. It just seemed like the breadth of work going on was detracting from this most important effort. The upper management just couldn't think about all of these different areas and make the important decisions that were needed. Although I don't really think so; we could have just grown bigger.

As it happened, we decided in about 1983 or '84 to have five major projects. We appointed a head of each of these major projects, and then we pared down all the rest. There were also some basic research projects that might end up being one of the next major projects. But we just had to get rid of the Genencor-type projects because it was just too distracting, according to the board. It turned out to be a very good solution to form another company. Herb Heyneker, one of our major scientists, and some of our business guys joined that company. They had a totally different kind of clientele, as you would imagine. One of their products is for cleaning contact lenses. So their whole interest and focus was different, so it just made sense for them to do it separate from Genentech, the up-and-coming pharmaceutical company. Then we had the animal health which we tried to sell off also. We ended up selling off certain projects and then gave up on that.

Vaccines

Kleid: I was most interested in the vaccine area. That was ended in '85, except for a couple of vaccines. That was very disappointing to me because it had the same kind of technology, and the products were really easy to make. These projects were in the pharmaceutical area, and they

each had a huge delta. You only had to make a tiny bit per vaccination dose. I was very disappointed that we gave up on a couple of projects. One in particular was the hepatitis vaccine, which actually was one of the five major projects. That one was far down the road. We had a complete process developed; we had clinical trials about to begin. The company decided just to quit.

Hughes: Why?

Kleid: I don't know all the reasons, but the part that really made me sad was the market analysis. The marketing people said that Merck was dominant, and they were going to be a 90-percent market share leader, and they were only going to get about $10 million per year, they estimated. It turns out that Merck's hepatitis vaccine has outsold all of Genentech products combined, every single year, up until a couple years ago. In fact, it might still. It was just an enormous product. But the marketing people said that selling vaccines was a big problem because there was so many people you had to sell them to. Plus, we could only charge about a dollar per dose, but instead the hepatitis vaccine sold by Merck costs fifty dollars. So the marketing people completely missed it. They didn't see any delta; I think that was the major thing.

The original deal we made with Bob Swanson was that Bob said, "You [scientists] figure out what you want to do and how to do it. If you succeed, I'll figure out how to market it; I'll figure out how to sell." But with the vaccine projects he kind of let us down.

Hepatitis B Vaccine

Yeast and Chinese Hamster Ovary Cell Culture

Hughes: Chiron was using yeast for hepatitis B vaccine. What were you using?

Kleid: We were using Chinese hamster ovary cells. We also had a yeast project. Actually, this particular project has been the subject of one of these interferences, which went on for over a decade. It's a very interesting story.

Hughes: Go ahead.

Kleid: Originally, Bill Rutter and Howard Goodman at UCSF started working with Merck on cloning the gene for the hepatitis virus. Eventually, they sequenced the whole gene and found the gene for the surface antigen. Well, Genentech had a similar project with Institut Merieux, where we cloned the hepatitis virus. It was my responsibility. We were very much parallel with Goodman and Rutter and eventually [Pablo] Valenzuela. We got the hepatitis gene sequenced. But Genentech was interested in making a product; we didn't feel that just sequencing the gene was really patentable since a group from France was also right in there with the hepatitis virus sequence. When I tried to publish our work-up to that stage, our legal patent people said, "No, don't publish that. Why don't you get it expressed first and then you can publish it. Wait until we get that step."

We took the gene for the hepatitis surface antigen and put it in *E. coli*--just like we had done for insulin and growth hormone and several of our other projects--and turned on the bacteria, but nothing happened. The surface antigen protein has a bunch of very hydrophobic amino acids, and that one protein ends up being the major part of the membrane of the virus itself, so it has a very unique kind of structure to it. Its called the Australia antigen. The Australia antigen was found and isolated from some people that had been infected with hepatitis. The antigen is made up of a hundred or so of these surface antigen proteins made into this little tiny ball. We tried making that product in *E. coli*, and it wouldn't get made. We devised a system where we hooked it onto a fusion protein and expressed it, and the bacteria would simply stop growing. They would just quit. *E. coli* just hated that protein. It led us to decide that we needed to get this product secreted. As it was being made, it was poking itself into the membrane of the *E. coli*, and the bacteria couldn't divide anymore. So we thought, let's get it secreted. That's when our yeast group came, and when our bacillus group came, and when Art Levinson came.

Hughes: They were brought in specifically to do hepatitis?

Kleid: They were brought in to develop secretion, because we thought it might be useful for other things too. Hepatitis was one of the first projects for each of them. We used it in bacillus. It still wouldn't work. Art Levinson's very first project was to hook the hepatitis onto a vector and develop systems for mammalian cells. As you might know, nowadays we make almost everything from mammalian cells. And he developed the original vectors on this hepatitis project that we still use today.

Hughes: Did Levinson come from UCSF with the Chinese hamster ovary cell technology in his pocket, so to speak?

Kleid: No.

Hughes: He developed that here?

Kleid: He developed that here with another scientist, Chris Simonsen, who came from Stanford. His group worked on transforming Chinese hamster ovary cells and making stable transformants.[1] Prior to this time there was quite a bit of work going on with COS cells, where you put plasmids in cell culture, and then see what happens over time.[2] It's called transient expression. But if you're going to have a process, you need a permanent cell line, because you need to be able to take the cell line out of the freezer, put it into the fermenter, grow it up, and make a product out of that. So that last step needed to be worked out, and it was worked out with hepatitis. We developed a cell line that made a huge amount of this hepatitis surface antigen

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[1]AD Levinson, "Expression of heterologous genes in mammalian cells," *Methods Enzymol.* 185, 485-7 (1990), and Levinson et al. U.S. Patent 5,011,795.

[2]CC Liu, D Yansura & AD Levinson, "Direct expression of hepatitis B surface antigen in monkey cells from an SV40 vector" *DNA* 1, 213-21 (1982) and Levinson et al. U.S. Patent 4,741,901.

particle, and it was extremely potent in all the tests we did.[1] We did the same thing with yeast and found a very poorly immunogenic product.[2] But we could make some.

Approaching Merck for Partnership

Kleid: Before we filed the patent applications on these two processes, one for CHO cells and one for yeast cells,[3] Genentech decided "maybe we don't want to do this project anymore; we've got to find a partner." Swanson insisted that we go to Merck and tell them about our progress and get them to support this project. So Art Levinson went to Merck in July of '81 and told them all about our work, not knowing that they had a similar project with Rutter. It turned out that that very month Rutter had some success with the yeast; it was the first time that they put the hepatitis surface antigen encoding vector into yeast cells.[4]

The way the story really goes is that at Genentech our guys Ron Hitzeman and Frank Hagie, using the interferon-encoding DNA and working with Ben Hall at University of Washington, made vectors that you could put into yeast cells. They worked out the system using interferon, and the University of Washington together with Genentech filed a patent on that system.[5] Then they said, "Okay, let's do hepatitis next." Ben Hall, who was working with us on the yeast expression project, said, "No, I have an agreement with Genentech that says that we'll work on the model system for interferon, but if you Genentech want to use it for anything else you have to get my permission first. By the way, I'm not going to give you permission. I'm going to go work on hepatitis with Dr. Rutter." So he took his marbles to UC.

But I didn't know about this "agreement." I got the vector that Ron Hitzeman's and Ben Hall's groups had made from Frank Hagie, and my technician put the hepatitis gene in there in place of the interferon gene.. We were going to test this thing in yeast, when unbeknownst to

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[1]EJ Patzer, GR Nakamura, CC Simonsen, AD Levinson & R. Brands, "Intracellular assembly and packaging of hepatitis B surface antigen particles occur in the endoplasmic reticulum," *J. Virol.* 58, 884-92 (1986).

[2]RA Hitzeman, CY Chen, FE Hagie, EJ Patzer, CC Liu, DA Estell, JV Miller, A Yaffe, DG Kleid, AD Levinson & H. Oppermann, "Expression of hepatitis B virus surface antigen in yeast," *Nucleic Acids Res.* 11, 2745-63 (1983) and Hitzeman et al. U.S. Patent 4,803,164.

[3]Levinson et al. U.S. Serial No. 298,235 filed August 31, 1981 (now US Patent 4,741,901 "Preparation of polypeptides in vertebrate cell culture") and Hitzeman et al. U.S. Serial No. 298,236 filed August 31, 1981 (now US Patent 4,803,164 "Preparation of HBsAg in yeast).

[4]P Valenzuela, A Medina, WJ Rutter, G Ammerer & BD Hall, "Synthesis and assembly of hepatitis virus surface antigen particles in yeast," *Nature* 298, 347-50 (1982) ,and Rutter et al. U.S. Serial No. 289,915 filed August 8, 1981 (now US Patent 4,769,238 "Synthesis of human virus antigens by yeast").

[5]RA Hitzeman, FE Hagie, BD Hall & G Ammerer, U.S. Serial No. 06/237,913 filed February 25, 1981 (now US Patent 5,854,018 "Expression of polypeptides in yeast").

me Ron Hitzeman told Tom Kiley, "Dennis has put the hepatitis gene into this yeast vector and Ben Hall won't give me permission to do that. What are we going to do?" So Tom Kiley told Ron Hitzeman to throw my stuff away; we didn't have permission to do that. Tom talked to Ben Hall and the attorney from the University of Washington, and they said, "No, we're not going to let you do that." But neither Tom nor Ron told me anything about this. Tom instead told Ron to make a new vector completely here at Genentech. So Ron and Frank Hagie proceeded to do that. Rutter and Hall went ahead and used the vector tested at Genentech.[1] But it turned out that our repeat was four weeks later than Rutter's and they filed their patent application a few of weeks before us.[2]

When we got the yeast and CHO-cell-derived hepatitis systems to work, we talked to Merck about it. Merck was extremely interested in yeast, but they just didn't seem to care about this CHO stuff, which floored Art, because this was working really well, and the yeast was working kind of mediocre--it wasn't very immunogenic. Merck eventually told Genentech, "Since we also work with UC, we'll pay whoever gets it first a nice big royalty. But we're not going to pay anything up front, and we're not going to support your project in the meantime." So that pissed Swanson off; he didn't want to work with them. All we asked for was something like $10 million for our project and a very small royalty on sales.

In the meantime, I guess Merck told Rutter, "You'd better get your patent filed." Within a week after Levinson's trip, UC filed their patent application, and we filed ours three weeks after that. This story has been gone into ad nauseum in an interference litigation. All the inventors and all the people involved with Ben Hall and Rutter gave depositions on what they did and when, and we went through all the notebooks. We presented our case, that although Rutter did it first, Genentech had the idea first, but we came in second because we had to make this vector all over again. The patent office decided that no, we didn't prove an earlier conception because we didn't have all the details. They said that we didn't know that yeast was going to work and make the surface antigen into particles. We said, "What are you talking about? The vector that we made they used and it works perfectly. So we had a perfectly good idea."

Legal and Production Problems

Kleid: We appealed that decision to the Court of Appeals of the Federal Circuit, the highest court you can go to in patent law, and they basically agreed with our facts but we lost anyway.[3] They said

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[1]The pFR vector, F and R standing for Frank and Ron, is used in the first examples in Rutter et al. U.S. Serial No. 289,915 filed August 8, 1981 (now US Patent 4,769,238 "Synthesis of human virus antigens by yeast").

[2]August 8th vs August 31st 1981.

[3]Hitzeman vs Rutter 58 USPQ2d 1161 (Fed Cir 2001) at 1169: "Only by demonstrating that he had a definite and permanent understanding as to whether and how the yeast would produce the 22 nm particles could Hitzeman establish conception of the particle size and sedimentation rate limitations prior to reducing the invention to practice. [2] The defect in Hitzeman's case is not that his "hope" was

that we had the idea of using our vector for hepatitis first, and we hoped to make it in the particle form, except for one thing: They basically said, "This invention is so fantastic you could not have any reasonable expectation that it would have worked and given hepatitis B surface antigen particles that had the same size and sedimentation rate of the authentic stuff. So although you had a great idea, you got what you wanted--in the end your idea did work--you didn't have any expectation that it was going to work. Your own inventors when asked, "Did you think it was going to work?" said, "Well, we hoped it was going to work." "Did you know it was going to work and give hepatitis B particles of the same size as the authentic?" "No."

That was right-- no, we didn't know it was going to work ahead of time.[1] So they basically said, "Well, you didn't have a conception because the idea was too fantastic." Usually, when you have a great idea, and you have clearly documented the day you got the idea, then if that idea turns out to work down the road, then that's your conception day. They changed the law completely, saying, "No, not only do you have to have a completely new idea, you needed to know it was going to work before you did it." And that smacks of obviousness, because its sort of like saying, "Well, you knew the invention was going to work before you started it, so that idea has to be old or obvious."

Hughes: Did Genentech make the point that if they'd known the invention was going to work, it would have been overruled as obvious?

Kleid: Exactly. So today the law is that if its about something really exciting and new, then you have to know that the invention is going to work before you have a complete conception.

The UCSF group never even participated in the tissue culture approach to hepatitis B, and that would produce a better product. We eventually licenced our hepatitis inventions on the CHO cell and on the yeast cell process, and we do get a modest royalty from Merck and Glaxo-Smith-Kline on the hepatitis vaccine. UC gets a huge royalty. It's the biggest royalty-producing invention in the UC system--by about a factor of ten.

The other disappointing thing is that the product from yeast isn't folded up particularly well. You have to oxidize it and do certain steps to make it fold well.[2] The tissue culture product is a more potent immunogen, and you would probably only need one shot or two shots instead of the three or four you need with the yeast product. But Merck's not interested in that because if it was more potent there would be no need for booster shots, and they wouldn't make as much money. [laughs]

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uncorroborated. Written documentation of Hitzeman's hope on February 3, 1981 would not have changed the outcome of this appeal. Rather, the critical deficiency is that Hitzeman specifically claimed the result of a biological process (i.e., the expression by yeast of the S-protein, followed by the assembly of the S-protein into particles) with no more than a hope, or wish, that yeast would perform this assembly process that had never before been achieved in yeast. Such a bare hope is insufficient to establish conception."

[1]Actually only a small fraction of the hepatitis surface antigen made inside yeast ends up as particles after being extracted from the cells, but that feature of the invention ended up in the claims.

[2]Wampler et al. "Multiple chemical forms of hepatitis B surface antigen produced in yeast" *Proc. Natl. Acad. Sci. USA* 82, 6830-4 (1986).

Hughes: Was that the last vaccine that Genentech was involved with?

Kleid: Well, we continued to work on the AIDS vaccine for quite a while, and that was the only exception to our leaving the vaccine area. We had research projects on rabies, on influenza, on herpes, on hoof-and-mouth disease vaccine, which I worked on. You've talked to Dan Yansura about that. So we had five vaccine projects, and they were all dumped, and AIDS became the only [vaccine] project after 1985. We had several products that we were hoping would be used for the treatment of AIDS, but we ended up with just this vaccine thing that became GenVax.

Hughes: Now VaxGen.

Kleid: VaxGen, sorry.

Hughes: So Genentech is not a vaccine company.

Kleid: And it won't be.

Herceptin is an antibody against a particular protein, and there's been quite a bit of work in animals about using the protein that Herceptin binds to, to induce antibodies, rather than treat people with humanized antibodies themselves. We've done a little bit of work on that, but not too much. So we've been mostly interested since the early 1990s in the other part of immunology--making the antibodies rather than inducing the antibodies. Immunology is still the dominant area at Genentech. Even the interferons have to do with improving the immune response. Our biggest impact has been in immunology.

Thymosin

Hughes: That relates to the next topic, thymosin, which was also supposed to be an immune stimulant, was it not?

Kleid: Right. The amino acid sequence was published in *Science* magazine in the late seventies by [Allan L.] Goldstein. Genentech decided, after somatostatin, that thymosin might be a good product to make the gene for.

Hughes: Why?

Kleid: Because it was small, thirty-or-so amino acids, and the sequence was known. It was a protein of the thymus gland, and the thymus is supposed to be involved with stimulating the immune system. So we thought that we would synthesize the gene, and it would be Genentech's first completely synthetic gene as opposed to the Genentech-City of Hope collaboration [on somatostatin]. In growth hormone, the front part was made at City of Hope, and the insulin A- and B-chains were made at the City of Hope. Thymosin was made in our own chemistry labs by Roberto Crea's new Genentech team. The gene was cloned by Herb Heyneker, and then it was hooked up with the tryp promoter just the same as somatostatin and the A-chain and B-chain of insulin. We were able to make a lot of that product. It doesn't have any methionine in it, so you

could cleave it with cyanogen bromide and make the protein. Ron Wetzel developed a process for purification.[1]

So now we had the gene cloned, the process for making it--everything. The only thing missing was what does it do? It is a human protein, and there was no animal model for its activity. You couldn't put it in a mouse and say, "Well, what's going to happen to the mice?" because it's a human protein. So the only thing you could conceivably do is put it in people and see what happens. So Nowell Stebbing's idea was, let's find some cancer victims and shoot them up with this stuff and see if their cancer goes away. And Bob Swanson said, "Do you know how much clinical trials cost? You're wanting to do a completely blind clinical trial? You just can't do that."

Trying to spin off that product to another company also turned out to be difficult. We had thought we were going to have a patent on it, and then we could license the patent. But it turned out the sequence was already known and published by Goldstein, so we couldn't patent the product. We could have a patent on the DNA and a process to make it. So we applied for patents on the amino acid sequence with a met in front. Then it turned out that Bruce Merrifield[2] synthesized thymosin one amino acid at a time on a polymer support and wrote a patent on making thymosin that way. But he claimed it very broadly and he also mentioned the met. So we couldn't get a patent on our met product either. So now there was no process license, so it just ended up being a complete zero.

We learned a lot from that. One, when you go to make a product, let's first try to figure out what it's good for. Two, Goldstein was our consultant, and he was helping us along the way. But when we had the patent battle about who did this thing first, although he was a co-author on the paper, he switched sides. It turned out he was already working for Roche, and it was Roche working with Merrifield. So he was our expert, but then he said, "No, Merrifield did this first, not you guys," at a very inopportune time. So we learned a lot from that project.

Hughes: Did you also learn to look ahead and try to gauge the patent situation? In retrospect, it looked as though the field was pretty well covered.

Kleid: On that particular molecule, yes. We were starting to run up against our own inventions too. We invented expressing in *E. coli* foreign proteins using an *E. coli* promoter. But that was for all proteins; that would not be new for thymosin. We couldn't patent a thymosin semi-synthetic gene because we had a patent application on making all semi-synthetic genes. And synthesizing genes was already patented, so it wouldn't be a new idea to add thymosin to the list. So our own references start to get in the way. The product was already known, and the process was no longer new due to our own patents, except for maybe putting a met in front of this thymosin, giving N-met-thymosin--and that was claimed by Merrifield!

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[1]R Wetzel, HL Heyneker, DV Goeddel, P Jhurani, J Shapiro, R Crea, TL Low, JE McClure, GB Thurman, AL Goldstein "Production of biologically active N alpha-desacetylthymosin alpha 1 in Escherichia coli through expression of a chemically synthesized gene," *Biochemistry* 19, 6096-104 (1980).

[2]Robert Bruce Merrifield won the Nobel Prize in Chemistry in 1984 for the development of methodologies for the chemical synthesis of polypeptides on solid supports.

Thymosin actually was the end of making products of known amino acid sequence via chemical synthesis of the DNA. From then on, everything Genentech has done has been on a product or protein that we didn't know what the sequence was. Nobody knew what the sequence was for the interferons or for tPA. So we could get a patent on the products themselves.

The Interferons

The Research Process

Hughes: All right, the interferons, in brief.

Kleid: Well, the interferons were going to be Genentech's ticket to going public. They were going to be a billion-dollar product, and Genentech had the inside track. We had the best collaborator, Roche. They had been making interferon, and they had a source for the interferon messenger RNA. Dave Goeddel got the project to clone the cDNA for interferon from these particular cells that Roche had. One cell line was from David Golde, the "KB" cells. Those cells supposedly made a lot of interferon. Roche had other kinds of cells that made fibroblast interferon and leucocyte interferon.

For leucocyte interferon, we would take a person's blood and leukophorese out the leucocytes and stimulate the leukocytes to make interferon, then isolate the messenger RNA, then clone these huge libraries. Dave would make cDNA libraries from the leukocyte cells and end up with hundreds of thousands of colonies which we would then screen to see if we could find one that had the interferon messenger RNA. All of us would poke these colonies for him. You can't imagine how long it takes to take a stack of forty petri plates, each with hundreds and hundreds of colonies on it, poke each one with a toothpick, and make an array so that you could screen them. All of us did that. I spent hours and hours poking colonies for Dave's project. Eventually, we were able to find some positives. The first positive for fibroblast interferon, I believe, was at Roche.[1] Then we were able to make the first leucocyte one, but there was a big race with Biogen.[2] I'm sure Dave told you the story of [Charles] Weissmann versus Goeddel on the leucocyte interferon.[3]

Hughes: Yes, he did.

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[1]DV Goeddel, HM Shepard, E Yelverton, D Leung, R Crea, A Sloma, S Pestka, "Synthesis of human fibroblast interferon by E. coli," *Nucleic Acid Res.* 8, 4057-74 (1980).

[2]DV Goeddel, E Yelverton, A Ullrich, HL Heyneker, G Miozzari, W Holmes, PH Seeburg, T Dull, L May, N Stebbing, R Crea, S Maeda, R McCandliss, A Sloma, JM Tabor, M Gross, PC Familletti, S Pestka, "Human leukocyte interferon produced by *E. coli* is biologically active," *Nature* 287, 411-6 (1980).

[3]C Weissmann, "Gene cloning by press conference," *N. Engl. J. Med.* 303, 531-2 (1980).

Then gamma interferon was next,[1] and it was a similar story with thousands of colonies and finally getting that cloned. But Dave's the better one to tell you about that. It mostly involved brute force: taking cells, getting the messenger RNA out, purifying it as best he could, size fractionating it, making cDNA libraries of clones--thousands and thousands of them--and painstakingly searching through each one, doing hybridization tests to see which one had your gene in it.

Hughes: Were the three types of interferon quite different molecules?

Kleid: They were. They were generally the same length, around 120-150 amino acids. The leucocyte interferons turned out to be a whole family of molecules. There are eight or ten different molecules--I don't know the exact number--all closely related. Fibroblast interferon turned out to be one molecule, and gamma interferon turned out to be one molecule.

Roche Involvement

Kleid: But the interferons didn't turn out to have the huge market that we had thought. When you purify interferon and treat a cell culture with interferon and then treat that cell culture with a tumor virus, the interferon stops the virus. The protein has antiviral activity. So we thought, well, that's going to stop cancer, because cancer is caused by viruses, as we thought in those days. So interferon was going to cure cancer. But the biology wasn't understood at the macro scale because nobody had a big enough pure sample of interferon to test on people. They had extracts that had some interferon in it. All the biology that was done in those days was on these extracts, and you couldn't really learn very much. What we needed was a good, solid vial of the stuff to do the studies on. That was what we and Roche provided. Then you could really figure out what the biology was. Interferon was shown early on to be useful to treat hepatitis B, a viral infection. Now its major use is in the treatment of hepatitis C.

Hughes: Roche could make larger quantities of the interferon because it was using recombinant DNA technology?

Kleid: Yes, and they were already making, from a particular cell line, a whole population of interferons, a mixture, but they couldn't really get it characterized enough. Together with Roche, we made a bacterial cell line that made one of the interferons, and they were able to scale that up, not unlike Lilly in regard to human insulin. Roche had plenty of expertise there and large-capacity fermenters, and they developed interferon alpha-1 into the product that it is today.[2]

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[1]PW Gray and DV Goeddel, "Structure of the human immune interferon gene," *Nature* 298, 859-63 (1982).

[2]Hoffmann-La Roche's Roferon-A was approved by the FDA for marketing in early 1986 for the treatment of hairy cell leukemia. It was the third recombinant human therapeutic to receive FDA approval. All three were developed by Genentech and its partners (Eli Lilly - human insulin, Kabi - human growth hormone, now Roche - human interferon).

Hughes: I read that by 1982 Goeddel and his colleagues had cloned eight interferon genes.

Kleid: Right, it turned out to be this family. Once he found one part of one gene, the idea was to get a full-length clone and to characterize it. But the various full-length positive clones turned out to be slightly different in DNA sequence and restriction patterns, and so he said, "Well, this must be another interferon." So he kept searching and searching and with one probe was able to fish out a number of related molecules, and then he made this whole collection of different interferon genes.[1] So it turned out to be a couple of years worth of work, sorting all that out.

Hughes: How did Swanson react when thymosin and to a large extent the interferons failed as products? The interferons were hyped as potential blockbusters, not just by Genentech, but by--

Kleid: Biogen.

Hughes: Yes, and other companies, too.

Kleid: These things don't die in one day. Except for one rare form, interferon did not work for cancer in humans, and further clinical trials was very disappointing. But Roche and Schering[2] kept forging on to see what the biology really was. We've gotten quite a bit of royalties on interferon.

Hughes: Has it been profitable?

Kleid: Oh, absolutely. It's a billion-dollar product. A lot of it has to do with the people that got non-A, non-B hepatitis.

Hughes: Hepatitis C.

Kleid: Hepatitis C.

Hughes: Sidney Pestka was Genentech's contact at Roche for interferon.

Kleid: Right.

Hughes: And there were some problems working with Roche.

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Kleid: There was a little competition between Dave's group and Pestka's group. We did end up with some individuals from Roche working at Genentech.[3] So there was quite a bit of cross-information going back and forth. It has more to do with working with Dave, I think. Dave is

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[1]DV Goeddel, DW Leung, TJ Dull, M Gross, RM Lawn, R McCandliss R., PH Seeburg, A Ullrich, E Yelverton, PW Gray "The structure of eight distinct cloned human leukocyte interferon cDNAs" *Nature* 290, 20-26 (1981).

[2]The licensee of the Biogen/Charles Weissmann interferon project.

[3]Mitch Gross and Robert Hershberg are two that I recall.

extremely competitive--and we've talked about that before. When you're on his team, it is just fantastic: "We are going to wipe out everybody else. We're going to do this and this, and we're going to be the champs. No question." But if you're in the next room from Dave, or you moved over a bench, all of a sudden you are competing with him. Pestka was on the East Coast! I understood that very well. For example, I knew that when I switched from being in the same lab and the same office with Dave to a different lab and a different office that I would end up being in competition with Dave rather than being on the same team. I was very disappointed, but I knew that was going to happen and sure enough it did.

The interaction with Pestka was the same thing: "We are better than him and we're going to show him that we can do this faster than he can." When you talk to Dave about this you can see how much competition he really felt. When you probe, "Why was Pestka no good?" you'll find very vague reasons.

Tumor Necrosis Factor

Hughes: Well, should we move on to tumor necrosis factor?

Kleid: Well, that's another Goeddel project--and Ed Nedwin's. One of Dave's postdocs was a major guy on that. And Cynthia Robbins. Have you ever heard of Cynthia Robbins?

Hughes: Robbins-Roth?

Kleid: Cynthia Robbins-Roth. She used to be a technician here at Genentech. Her project was tumor necrosis factor. The assay for tumor necrosis factor was very cumbersome. So what you had to do in order to clone tumor necrosis factor, as with interferon, was to purify messenger RNA. Then there was a very cumbersome assay to make protein from the messenger RNA sample and then assay that protein for tumor necrosis factor activity. It took a long time at each of these steps.

Cynthia eventually got a sample of messenger RNA that looked like it was going to be the right thing. Then Dave Goeddel and the others cloned it. It turned out to be, after a large amount of effort, some bovine protein. So she was immediately branded as not knowing anything about anything. It had to be done over again, and it was eventually done by Nedwin, working with Dave very closely. I think Diane Pennica actually worked on that project also. Nedwin is now the president of a company near Davis, in the Sacramento Valley. At any rate, they eventually were able to clone the cDNA for tumor necrosis factor.[1] The protein had a very interesting activity: You could inject this protein into a tumor and the tumor would necrose. That's how it got its name, tumor necrosis factor. That sounds like something you'd want to sell, right?

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[1]D Pennica, GE Nedwin, JS Hayflick, PH Seeburg, R Derynck, MA Palladino, WJ Kohr, BB Aggarwal, DV Goeddel "Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin" Nature 312, 724-9 (1984).

Hughes: It sounds pretty good against cancer.

Kleid: Right. So they were very, very excited about that project. Tumor necrosis factor and gamma interferon became our lead things for cancer. The idea of injecting a tumor and seeing it necrose turned out to be a false hope at the time because tumor necrosis factor just wasn't understood very well. For thymosin, tumor necrosis factor, and gamma interferon, there wasn't enough human biology data to just go out and try it in people. Where do these molecules fit into cancer treatment? Completely unknown--but let's just try them anyway, that was the attitude. Tumor necrosis factor creates a toxic reaction. When one very famous cancer researcher got cancer--I think he was at Sloan-Kettering--they treated him with tumor necrosis factor, and he died instantly. It killed him.

When we started clinical trials with tumor necrosis factor, we started at an extremely low dose, and it was toxic. It's a very, very powerful protein. We very gradually increased the doses. In fact, my wife, Michele, was the CRA, the clinical research associate, on this project. She worked with Dr. Steve Sherwin who developed the program to try and develop tumor necrosis factor and gamma interferon into cancer treatments. At the end of the day we weren't able to use them for cancer treatment at all. It was just too early in our understanding.[1]

Emphasis on the Biology of Drug Activity

Hughes: After your initial successes with somatostatin, insulin, and growth hormone, you ran up against the biology.

Kleid: Exactly.

Hughes: Did that come as a shock? Was Genentech's initial expectation that you could synthesize DNA, you could apply recombinant DNA, and that's all you needed to know?

Kleid: It wasn't a shock to me. [laughter] But in the company we were extremely weak on biology pre-1984. We had the technology for the chemical synthesis of DNA and for cloning and for making the proteins, and we could make anything, even these rarest of rare molecules. Now what do you do with them? What biology, what systems do you use them in? We had nothing.

Prior to 1983, the head of biology was Nowell Stebbing. Nowell seemed like a very bright guy. He came from the UK. He was in the middle of getting the growth hormone clinical trials started. As you know, the growth hormone was pretty toxic when it first came out. That was under his watch. Then thymosin--what were we going to do with that? Are we just going to test it randomly? The interferon clinical trials were mostly done at Roche. There was quite a bit of background knowledge on leucocyte and beta interferon. But when we came to gamma interferon and tumor necrosis factor, you're talking about molecules where there's no model at

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[1]After nearly twenty years of study, a lot more is understood today, see: G Chen & DV Goeddel, "TNF-R1 Signaling: A Beautiful Pathway," *Science* 296, 1634-5 (2002).

all. Where do we even start clinical trials? So the way I saw it, the clinical trials were just blind: Take somebody with cancer and see what happens.[1]

With immune interferon, we decided that we should clone the mouse gamma interferon and see in mice what the heck it is and where it fits in with the biology, because you can do those kinds of studies on those guys. There was a meeting of twenty or so scientists with Bob Swanson there, saying, "Why do we want to bother with this? Mice don't have any money." I said, "Look Bob, right now gamma interferon is crap. We have no idea what it is for. There isn't even a way to start to find out what it's for. You can shoot it up in people for cancer, okay fine; take a step in the dark, maybe you'll get lucky." They said, "Okay, let's do that. There's so much money to be made if it works for cancer; let's just go ahead and do that."[2] And of course it didn't work.

It turns out that various "anti-" tumor necrosis factor products are very important. The first anti-tumor necrosis factor product approved was the Immunex product for arthritis.[3] TNF is one of the mediators of arthritis. The Immunex anti-TNF product is the TNF receptor made to look like an antibody. So one end of the product is the TNF receptor; the other end is an antibody. Immunex developed the product. Genentech researchers developed the idea for this type of genetically engineered product, an immunoadhesin, when working on AIDS.[4] Enbrel is a major product in the world right now. It's one of the billion-dollar drugs.

Gamma interferon ended up being for the bubble babies who have no immune system at all.[5] There didn't turn out to be very many bubble babies so we eventually sold that product to Connetics. Connetics formed another company, InterMune, which has some ex-Genentechers. They have followed up on some really significant activities for this gamma interferon, so it is finally going to be a major product over the next decade.

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[1]Gamma interferon clinical trials began in earnest during 1984.

[2]According to Genentech's 1986 Second Quarter Report, a Phase I clinical trial for the "combination use" of gamma interferon and tumor necrosis factor began in May of 1986 which states: "the combination of the two products should be more effective than either one alone against certain cancers."

[3]Enbrel. For some of the basic research leading to this product see, A Ashkenazi, SA Marsters, DJ Capon, SM Chamow, IS Figari, D Pennica, DV Goeddel, MA Palladino, DH Smith, "Protection against endotoxic shock by a tumor necrosis factor receptor immunoadhesin," *Proc. Natl. Acad. Sci. USA* 88, 10535-9 (1991); PH Wooley, J Dutcher, MB Widmer & S Gillis, "Influence of a recombinant human soluble tumor necrosis factor receptor FC fusion protein on type II collagen-induced arthritis in mice," *J. Immunol* 151, 6602 (1993).

[4]A Ashkenazi, DJ Capon, RH Ward, "Immunoadhesins," *Int. Rev. Immunol.* 10, 219-27 (1993).

[5]Actimmune, which works by activating macrophages, is now being tested for difficult-to-treat infections, including mycobacterial disease, and also for idiopathic pulmonary fibrosis.

Evolving Infrastructure for Genentech Science

Informality Cedes to the Research Review Committee

Hughes: Talk about the interaction with Swanson, who was trained as a scientist, but he operated as a venture capitalist and then as the business brains of the company. What was the dialogue with him, particularly when you came up against roadblocks?

Kleid: He was not a scientist, although he read science magazines. He was in venture capital/business. In the early days, the scientists reported to Bob. We each had our own projects. But the control he had of what we were going to do was very, very weak. In the early days, we scientists decided what new projects were going to get started when and which projects were the most important. He was the cheerleader. But as far as control, it was like pushing a rubber band or something. Of course it wasn't that hard to get an agreement that insulin, human growth hormone, and interferon were important in the early days. But what would be next?.

We had a lot of meetings. We would have not only these ho-hos but we would have our directors meetings; our little department meeting would review what we were doing. We set up the Research Review Committee in 1981 where projects would be reviewed by a group of scientists. Bob would often come to these, as well as one of the attorneys. So we set up a little hierarchy to review projects.

Vice President of Research and Other Administrative Positions

Kleid: Then Bob decided it still wasn't quite enough, and he brought in a VP of Research in 1983, and that was Dave Martin.[1] It was about the time we set up these five major projects, pared down the number of research departments, and jettisoned the animal health and the enzymes and eventually even the vaccines. But that was mostly Bob working with Dave Martin.

All of us, prior to that time, were in charge of our own little area. Whether it worked or not, whether Genentech was successful or not, we felt it was on our own shoulders: "If my project works, then this company's going to have such a great future! If it doesn't ... " Now, with the addition of Dave Martin there was somebody else in charge, and we were all of a sudden postdocs. That's really what it felt like to me. Here was my boss, and he was telling me what I should do.

Hughes: How did that work?

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[1]Although never named vice president, Herbert Heyneker was the first leader of the research group at Genentech for a very brief period in 1979. See his oral history in this series. Giusseppe Miozzari took over that role during the next year or so. During 1980 several research departments were formed, molecular biology, headed by Dave Goeddel, and protein chemistry headed by Mike Ross, biology headed by Nowell Stebbing, and Roberto Crea's synthetic chemistry laboratory. [SSH]

Kleid: I didn't like it at all, to tell you the truth. We had a tremendous group of scientists in '83, especially the Ph.D.s on the molecular biology side, with Axel Ullrich, Peter Seeburg, Art Levinson, Herb Heyneker, Dave Goeddel, Dick [Richard. A.] Lawn, Ron Hitzeman, Diane Pennica,[1] and me![2] We had a group of scientists that was tops, absolutely tops, at what we were doing--cloning things and making these products in bacteria or tissue culture. We were so far ahead of the rest of the world. As individuals, we got invited to meetings all over the place. We were well-known scientists. All of a sudden we were postdocs again, and the responsibility for making Genentech a success was not ours; it was Martin's. In my view, it destroyed this synergy that we had. Swanson I don't think ever realized what he had and what he lost. Half were gone by the time Dave Martin was gone [1989]. The whole feeling of that group just disappeared.

Hughes: Were there not some meetings with Swanson protesting this new arrangement?

Kleid: What could you really protest? You had a new boss. You no longer reported to Bob; you reported to this guy who was creating the "vision" that we were going forward with.

If you look at our projects up through 1984, we led the world. From about '85 to '88 we did nothing in my opinion. On the development side, yes, we pushed through tPA and got growth hormone FDA approved. Factor VIII we cloned in late 1983 and sold off. In my mind these were grind-out kind of things, but as far as major breakthroughs there was nothing. We did spend quite a bit of time on AIDS, and we developed this immunoadhensin idea that works for Immunex now. But the innovators had to go through Martin. Martin was not a Ph.D.; he was an M.D. The worst thing you ever want to do as a Ph.D. is go work for an M.D. He was also one of the ones responsible, in my mind, for getting rid of the vaccines. I have a personal view on this, okay? It should be considered with a grain of salt. Maybe all these other people loved the guy. [laughs] You can go ask. In my mind, he took something away from the group that was never to be regained.

Then Bob hired Kirk Raab in early 1985 as COO [chief operating officer]. And then he hired a guy to head clinical, Ralph Snyderman in late 1986, who was also a very well-known M.D. At that time there was also Steve Sherwin, M.D.-- he worked on gamma interferon and TNF clinical trials. Barry Sherman, M.D. did the growth hormone clinicals. Later he was made head of the clinical area. But each of these three doctors had their own clinical research teams in the early 1980s. But they hired on top of those guys--Ralph Snyderman. He was a very famous guy. Martin, Raab, and Snyderman were fantastically expensive VPs. You can look in the annual reports from the late 1980s and see how much stock they got. It is absolutely astounding what these people got, and what they contributed during that three or four years you could write on the back of an envelope, in my book. Bob decided to let Raab take even more charge of the company. Raab became CEO, and Bob went on the board of directors. What

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[1] I forgot to name many of the other fine Ph.D.s we had in our group at that time: Dan Capon, Larry Lasky, Phil Berman, Rick Derynk, Dave Leung, Jane Gitschier, Wendy Colby, Herman de Boer, Dennis Henner, Mark Matteucci, Eric Patzer, Glenn Nedwin, Herman Oppermann, Mike Shepard, Chris Simonsen, Arjun Singh, Jack Obijeski, William Wood, and Pat Gray.

[2] Some of the notable non-Ph.D.s in Genentech molecular biology group during 1983, many of whom have gone on to get Ph.D.s and have also had notable careers: Lisa Coussens, Maureen Hoatlin, Dan Yansura, Bill Holmes, Tom Dull, and Douglas Smith.

happened to Kirk Raab and tPA are all wrapped up together. And then the ascendence of Art Levinson who is now the savior of the company and who changed things around a lot.

Interacting with David Martin

Hughes: What was the working relationship between Dave Martin and the scientists?

Kleid: Well, he had his favorites. I think Dave Goeddel got along with him very well and so did Art Levinson. Axel Ullrich to a lesser degree, and Seeburg to a lesser degree also. I don't know how he felt about me.

Hughes: What would happen if the relationship wasn't good?

Kleid: Well, in my case, I had a particular interest in immunology. He said, "You're not going to work on that anymore. I want you to study how bones are grown. You've spent ten years and now you're at the top in immunology. But I don't want you to work on that; I want you to start a new research area from scratch."

Hughes: What was his rationale?

Kleid: It was either that or I could go somewhere else.

Hughes: Martin thought somebody at Genentech should be working on bones?

Kleid: Yes. And since we weren't going to do the project I was working on anymore, I should go do that. I said, "No." I decided I was more interested in patents than in bones, so I got this job as a patent agent here in legal. Tom Kiley and the legal group that was working on patents were suddenly involved with patent litigation. I thought, well, if I could learn to speak the patent language and became a patent agent, then maybe I could help communicate the research to the litigation attorneys. I thought that it would be important for attorneys to understand the science. They need to explain complex science issues to juries and judges. First they're going to have to learn it themselves, so I'm going to help them understand this. I had been doing a bit of that with Kiley ever since he came on the scene and also with the other patent attorneys, so I was interested. It's a nice kind of academic type job because your students pay a lot of attention. So it has been extremely satisfying. Of course patents and patent litigation has a big impact on the economics of the company--whether our patents go up or down or whether we have to pay huge royalties on other companies' patents or not. So I feel like I'm doing something important.

Hughes: You also keep your finger in both pies: You follow the scientific process, yet work in the legal area.

Kleid: I'm following the science at a time distance. I probably know more about molecular biology research that occurred between '78 and '84 than anybody in the world. All of these projects, I know just about every single reference, everything that went on back at that time because I've

been studying research done in that time frame for the last fifteen years. It's really studying research back in time and then explaining it in terms of what we know today. I don't really have a lot of opportunity to study what Genentech is doing right now. I don't have time to go to the seminars and keep up with what's going on in the lab. Also, I'm not allowed to tell the scientists too much about the litigation because a lot of my knowledge comes from the other people's labs. I'm under protective orders, and I've agreed I will not disclose this information to Genentech scientists. I like the job. These fifteen years have been just as interesting as the ten at Genentech that went before. It's been really exciting.

Lymphotoxin

Hughes: May I broach one last topic for today--lymphotoxin?

Kleid: Yes. Lymphotoxin is in the same category as TNF and gamma interferon. It's another immune-response molecule involved with the immune system. It was a very tricky and difficult molecule to get cloned. The amino acid sequence wasn't known, and we had to develop assays and a source for the mRNA and clone it. Again, Dave Goeddel had something to do with lymphotoxin as well as Bart Aggarwal.[1] Bart Aggarwal was the protein chemist who got enough purified samples to get some amino acid sequence data so that we could clone it. He worked for the protein group, but also with Dave Goeddel's crew.

Urokinase

[Interview 5: January 25, 2002] ##

Hughes: Today we will start with urokinase, which I believe is the beginning of the trail to tPA.

Kleid: Yes, it is.

Hughes: Could you tell me about that project?

Kleid: Well, as I recall, Bob Swanson and Herb Boyer met with a European company, Chemie Gruenenthal, now called "Gruenenthal GmbH." Gruenenthal was making urokinase out of urine, as was Abbott. In the early days we had a list of all the human proteins that might be a target of this technology, and urokinase was on it. Urokinase was used for the treatment of heart

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[1]PW Gray, BB Aggarwall, CV Benton, TS Bringman, WJ Henzel, JA Jarrett, DW Leung, B Moffat, P Ng, LP Svedersky, DV Goeddel, et al. "Cloning and expression of cDNA for human lymphotoxin, a lymphokine with tumour necrosis activity" Nature 312, 721-4 (1984).

attacks in a procedure called thrombolytic therapy.[1] They would take a catheter and string it through the person's arteries near the heart and then inject a little of this urokinase or streptokinase and dissolve blood clots.[2] In 1980 or so, other companies were interested in making urokinase via recombinant DNA technology and getting away from this urine stuff. We ended up with a research project and signed an agreement with Gruenenthal. The plan was that we were going to get the gene cloned, the product expressed, purified and everything. The person in charge was Herb Heyneker. We looked for cell sources that would make urokinase mRNA, and then we would clone cDNAs made from mRNA from those cells to see if we could find a urokinase sequence.

Tissue Plasminogen Activator

Herb Heyneker, Diane Pennica, Desiré Collen, and the Genesis of the tPA Project

Kleid: Herb did a lot of reading about urokinase to see where he was going to start. He came across literature on tissue plasminogen activator. Tissue plasminogen activator is very similar to urokinase, except it has one major difference: it likes to bind to fibrin.[3] So when you have tPA around, it will seek out a clot, seek out fibrin, and start digesting. Urokinase didn't have that feature; it would just circulate. That's why you'd use a catheter and put it in the right spot for intracoronary thrombolysis. tPA, was being researched, and the very early literature on it was coming out. Herb said, "tPA sounds even more interesting than urokinase." We had this Gruenenthal deal on urokinase; we didn't have anything on tPA. But he thought, maybe we can do both.

We hired a young scientist from Hoffman-La Roche named Diane Pennica. Diane worked on messenger RNA isolation and had a project with a friend of mine, Jack Obijeski, from the Centers for Disease Control. He said, "She is really, really good with mRNA. You should interview her." So we brought her out here for an interview. She seemed like a sweet little girl, about 5'1", extremely bright, very motivated, and just seemed like she was going to fit here at Genentech perfectly, so we hired her.

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[1] AP Fletcher, N Alkjaersig, S Sherry, E Genton, J Hirsh, F Bachmann "The development of urokinase as a thrombolytic agent. Maintenance of sustained thrombolytic state in man by its intravenous infusion," *J. Lab. Clin. Med.* 65, 713-731 (1965).

[2] ER Gonzalez "Intracoronary thromolysis to abort heart attacks: wave of the future?" *JAMA* 245, 11-13 (1981); MJ Cowley "Methodologic aspects of intracoronary thrombolysis. Drugs, dosage and duration," *Circulation* 68 (2 pt 2), I 90-5 (1983).

[3] D. Collen "On the regulation and control of fibrinolysis. Edward Kowalski Memorial Lecture," *Thromb. Haemost.* 43, 77-89 (1980).

The day she came, Herb said, "Look, there's a meeting on tPA in a couple of days in Sweden, and all the major people will be there. Why don't you go to that meeting, because I can't go." So like the second day she was here she was on an airplane to Sweden. She's a Ph.D. and like I said, very bright and capable. She loves to tell the story of how she ended up at this meeting a day early because of a miscalculation of the time change and walked into a pre-meeting of the organizers and the senior people. She just walked right in. Like I said, she's 5'1 and looks seventeen. She joined in and as a result met one of the leaders on tPA, Desiré Collen from Belgium. They immediately hit it off, as anybody would hit it off with Diane because she's a person with a smile that you'd like instantly. They exchanged information, and she told them that Genentech would be interested in cloning the tPA gene, and that maybe we could work together.

Hughes: Was Collen the author of some of the early literature that Heyneker discovered?

Kleid: Yes. He was one of the ones that purified the first samples of tPA. They originally were purifying it from blood, but he found a very strange cancer cell line that was producing tPA, and he was able to purify it from that cell line.[1] This was called the Bowes melanoma cell line. This cell line, originating from a woman whose last name was Bowes, was developed at the Roswell Park Institute.[2] She apparently had a melanoma that was very serious. Dr. George Moore studied samples of the melanoma cells and got them growing in the laboratory. She would come to his laboratory to see the progress on his project. Dr. Moore told me that he was with her when she died. He developed this cell line, and over the next few years tried to figure out why the cells were so malignant. One of its properties was the production of a plasminogen activator.[3] Years later, after tPA was discovered, it was found to be producing tPA, and that's one of the reasons why [the melanoma] is so serious. I guess these cells sort of chew on neighboring cells, by virtue of the tPA being produced in large amounts by these cells.

Desiré Collen got that cell line and was able to make the first large samples of tPA suitable for testing in animals. He also did the first tPA thrombolysis study in a person, thanks to the Bowes cells.[4] He was just starting this work when Diane met him. Thanks to Diane, Genentech made an agreement with him to help fund his work and even grow up a lot of these cells and make a good enough sample of tPA to further pursue the idea that he was talking

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[1]DC Rijken and D Collen, "Purification and characterization of the plasminogen activator secreted by human melanoma cells in culture," *J. Biological Chem* 256, 7035-7041 (1981).

[2]JR Mitchen, GE Moore, RE Gerner, LK Woods, "Interaction of human melanoma cell lines with autochthonous lymphoid cells," *Yale Journal of Biology and Medicine* 46, 669-680 (1973).

[3]DB Rifkin, JN Loeb, G Moore, E Reich, "Properties of plasminogen activators formed by neoplastic human cell cultures," *J. Exp. Med.* 139, 1317-1328 (1974).

[4]W Weimar, J Stibbe, AJ van Seyen & D Collen, "Specific lysis of an iliofemoral thrombus by administration of extrinsic (tissue-type) plasminogen activator," *The Lancet*, November 7, 1981 1018-1020 (1981).

about.[1] The idea was to inject it into somebody and see if it would cure their heart attack. This intravenous injection would get away from the difficult intracoronary catheterization procedure. tPA would be better because it will circulate through the blood stream until it finds a clot, then it should bind and digest the clot.[2] You could just give somebody a shot and their heart attack would go away. People really didn't believe it. In the 1970s most cardiologists thought blood clots were a symptom of the heart attack rather than the cause. The arteries get narrower from atherosclerosis, then some ischemia would result causing the heart attack, and then blood clots would form. But now we know that what causes a heart attack is a little blood clot caught in that narrowed artery. You get a quick fix with the tPA. That was the theory, at least.

Hughes: Was there resistance early on from the cardiologists?

Kleid: There was a body of cardiologists that was resistant, but that was mostly in the seventies. In the eighties Desiré Collen had promoted the idea that this was happening. Of course, most cardiologists want to see the clinical studies. They say, "Great theory, but let's see the trial results." So I don't know how much resistance there was. He would know a lot more about that.

Hughes: So tPA had quite a history in terms of a possible therapy for heart attacks. Is that it?

Kleid: Plasminogen activators had been studied for a long time. Thrombolytic therapy began in the 1960s. But it was hard for them to figure out the details of the differences between urokinase and tissue plasminogen activator until the structures were determined by gene sequencing. It was only after that time that tPA became a focus and intervenous treatment replaced the catheter.

Hughes: What's the significance of "tissue?"

Kleid: I don't know how the name came about. Although discovered in the 1960s,[3] scientists in the 1970s figured out that "tissue" plasminogen activator had this special binding property to fibrin. Desiré put this theory together that you could cure heart attacks with that. I guess there must have been some resistance because our little cloning company in California [Genentech] was the only one to have enough interest in Desiré Collen's work to support his project of growing up a lot of these cells, isolating a good batch, and trying it out. Together, that's what we did. The very first clinical study was made with samples of tPA made out of these Bowes melanoma cells.

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[1]D Collen, DC Rijken, J Van Damme, A Billiau, "Purification of human tissue-type plasminogen activator in centigram quantities from human melanoma cell culture fluid and its conditioning for use in vivo," *Thromb. Haemost.* 48, 294-6 (1982).

[2]This is called thrombolysis. Thrombolysis procedures from the 1960s did not gain acceptance until the 1980s. *Compare:* AP Fletcher et al. *J. Lab. Clin. Med.* 65, 713-731 (1965) *with:* ER Gonzalez "Intracoronary thrombolysis to abort heart attacks: wave of the future?" *JAMA* 245, 11-13 (1981).

[3]CS Kucinski, AP Fletcher, S Sherry "Effect of urokinase antiserum on plasminogen activators: demonstration of immunologic dissimilarity between plasma plasminogen activator and urokinase," *J Clin. Invest.* 47, 1238-53 (1968).

The Research

Kleid: Diane and Herb Heyneker were the leaders and isolated messenger RNA from the cells and tried to clone the tPA cDNA from that. That turned out to be very difficult.[1] The amount of tPA made by these cells was really low, and the amount of message was really tiny.

Hughes: Your standard is previous amounts in Genentech projects?

Kleid: Messenger RNA for pituitary growth hormone was maybe 10 percent, but you could enrich it to 80-90 percent. Interferon, we thought, was like one in 1000; it turned out to be one part per 100. TPA was about the same as urokinase, like one message in 3000, and that's even in these cell lines that are making this. So it's a pretty raré message.

You make cDNA from all the message and then you get complex mixture, and after cloning you get a "library" of clones. In this case you would make thousands and thousands of clones and find out if any of them have tPA encoding sequences. Diane isolated the message and then fractionated it into different size classes. What she was good at at Roche, was purifying message, getting it out of the gel, and making a sample of this pure message. You had to have very careful techniques to do that because it's really easy to get degraded message. She figured out a way to do that and then assayed the samples and found out the approximate size of tPAs message. It turned out to be very long, about a third longer than it should have been. It was pretty hard to do.

Then, how do you find the clone? You're not going to take each one out and sequence it. And, besides, you don't know the sequence. So they got a sample of tPA protein from Desiré Collen. One of our protein chemists, Bill Kohr (who was also an inventor on this), chopped the tPA into pieces and sequenced the little bits.[2] He had about fifty or so little pieces of tPA. The amino acid sequencer sequenced one amino acid at a time from the N-terminal end, and that study gave data for maybe five to ten amino acids in a row from some of the many tPA pieces he had. After five or ten sequencing cycles, the background would wipe out the ability to read the data. Bill found a sequence that spelt WEYCD (pronounced "wicked"). The number of codons that code for each amino acid was pretty rare in that particular sequence; I think there's only one codon for W. So we made a whole batch of oligonucleotides for each DNA sequence that encoded this WEYCD amino acid sequence and then radioactively labeled that DNA and used it for a probe to screen all these clones to see if any of them would light up with that probe. That's what Diane did in this <u>big</u> experiment. It took weeks to do that. It looked very

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[1]D Pennica, WE Holmes, WJ Kohr, RN Harkins, GA Vehar, CA Ward, WF Bennett, E Yelverton, PH Seeburg, HL Heyneker, DV Goeddel, D Collen, "Cloning and expression of human tissue-type plasminogen activator cDNA in *E. coli*," *Nature* 301, 214-21 (1983).

[2]GA Vehar, WJ Kohr, WF Bennett, D Pennica, CA Ward, RN Harkins, D Collen, "Characterization studies on human melanoma cell tissue plasminogen activator," *Bio/Technology* Dec. 1984, 1051-1057.

impressive at the end. She had these huge films with all these dozens of spots, and some of them look a little bit darker than other ones. Diane switched from working with Herb Heyneker to Dave Goeddel because this was taking a little too long, or she was getting frustrated or whatever. She switched over to work with Dave Goeddel, and they figured out which spots were the most likely to have the DNA sequence that they wanted. From that experiment they chose the clones that they wanted to test for tPA DNA sequences. They sequenced a whole bunch of them and then eventually found one that had the WEYCD sequence in it.

Hughes: Was there a rational basis for choosing which peptides to sequence?

Kleid: No, Bill just sequenced them all until he came up with data from one or two tPA fragments that had an amino acid sequence that didn't have too many redundant codons. For example, lysine wouldn't work very well because there would be six different choices for codons. But this WEYCD turned out to be the key.

Hughes: And there was only one codon for each of those?

Kleid: Each of these amino acids had about two codon choices each. I think in the end there would be eight oligonucleotides fourteen nucleotides long. Among those there would be a match to all of the possible codons for the WEYCD sequence. They used that probe and found a chunk of cDNA that encoded part of the messenger RNA, and then they used that cDNA as a probe to find more. It turned out that there were very few others. Then they compared the sizes of the inserts in the clones and found the longest one. But none of the clones turned out to be full length. All the clones they made kept ending at a certain point. They couldn't get the whole thing. It seemed that when reverse transcriptase and DNA polymerase copied the messenger RNA and made double strand cDNA, the polymerase enzymes kept running out of gas or something before they got to the full-length mRNA end. So they did a special trick to get the last part of it. To make a very long story short, they finally got the whole cDNA sequence. Then we put the gene into *E. coli* to make tPA. So now everybody's happy. Okay, we've got this fantastic thing.

At about that same time, Desiré Collen came in with the news of patients with a coronary thrombosis that had been given Bowes melanoma cell-derived tPA.[1] Everybody was getting very, very excited about that except for one thing: Could *E. coli* make any of the protein? The *E. coli* just didn't want to make it very well. It's a really long protein. They drew the structure and it had kringles in the amino acid sequence where there are all these disulfide bonds. It was a very complicated molecule.

Hughes: *E. coli* didn't know how to make it?

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[1]F Van de Werf, PA Ludbrook, SR Bergmann, AJ Tiefenbrunn, KA Fox, H de Geest, M Verstraete, D Collen, BE Sobel, "Coronary thrombolysis with tissue-type plasminogen activator in patients with evolving myocardial infarction," *N Engl. J Med.* 310, 609-13 (1984).

Kleid: That's right, not very well, just tiny amounts were detected.[1] Then Dave Goeddel and Art Levinson along with Diane Pennica and Liz Yelverton put the gene in a vector that would work with tissue culture cells.[2] That related to Art's work on hepatitis. He developed a vector for hepatitis B surface antigen expression in CHO cells, and that vector would be used to make tPA. This was required in order to make the tPA with the correct structure. Now we really needed that process.

Bob Swanson was very, very nervous about this. At the time, we cloned the gene and were making a tiny bit of it in *E. coli*. We filed a patent application on May 5, 1982 that explained how we made tPA in *E. coli*. We filed the application before a paper this time because this was really important. By a few weeks later we made a vector for tissue culture cells, and that would turn out to work very nicely. But we kept working on the *E. coli*-derived material that whole summer of 1983 and into the fall, trying to refold the molecule because *E. coli* just made the protein into refractile bodies, similar to what we faced with growth hormone. But luckily, along side of that project was the CHO cell tPA project. Using tissue culture we didn't need any refolding to make active tPA; it was making it already. So we thought: We have the Bowes melanoma cells; they're making some tPA. But these CHO cells might be much better. True they were still tissue culture cells. But because we had the gene and we could amplify the gene inside the cells and make lots of copies of the gene, we might be able to up the yield. Using this amplification process we selected a tissue culture cell line that made lot more tPA than the Bowes melanoma cells, but unlike the Bowes, this new cell line would not be a human cancer line. So this system had a lot of advantages over Bowes cells. But we had one big problem: our manufacturing people only knew how to grow *E. coli* on large scale!

Designing Cell Cultures

Kleid: We had just finished building a factory to make products from *E. coli*. So we had these 10,000-liter fermenters all ready to make Genentech's next product after growth hormone.

Hughes: The factory was built for tPA?

Kleid: That's right; tPA was next. Recall, we were working on gamma interferon at that time, but the clinical trials were not going that well. We had sold off leukocyte interferon (also known as alpha interferon)--Roche was going to make that. We had licensed growth hormone outside the U.S. We were going to make growth hormone for the U.S., but that was all that was looking good. So tPA was the next one. Here's our brand new factory designed for lots of *E. coli* products, certainly more than just growth hormone. That was supposed to be just a little product. We had lots of space for more products. So we built this nice big factory, but how

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[1]These amounts were characterized as "de minimis" during a later patent litigation.

[2]AD Levinson, D Pennica, WJ Kohr, GA Vehar, DV Goeddel, EM Yelverton, CC Simonsen, "Human tPA production using vectors coding for DHFR protein," Patent Application USSN 06/459,153 filed Jan. 19, 1983, later issued as U.S. Patent 5,011,795.

were we going to make tPA in there? We couldn't do it in *E. coli*; we had to use tissue culture cells.

At that time, production using tissue culture cells required roller bottles. The media's very expensive. You need fetal calf serum to make these cells grow, and the serum was very expensive. There wasn't any way to get rid of the fetal calf serum and still have the cells grow nicely in those days. Nowadays, we've figured out what the fancy ingredients are in fetal calf serum. But in those days you grew tissue culture cells in a little bottle that was slowly rolling in fetal calf serum so that the cells would coat the inside of the roller bottle in a thin monolayer. Then the media would soak on these cells and a little tPA would come out into the media. So if you rolled these roller bottles for a couple of days, collected the media, then you could isolate some tPA from the media.

Hughes: Was that roller bottle technology developed elsewhere?

Kleid: It was. Some of the original work on interferon from cell lines used that technology to make interferon for research. But nobody had thought about making a pharmaceutical that way. But we decided to go ahead and try it, and we built a whole "warm" room full of roller bottles and developed a process to make tPA in roller bottles. We actually made enough to do our first clinical studies.

Hughes: Was Art Levinson leading the charge in terms of the cell culture?

Kleid: He was on the molecular biology side. We hired some people that had done large-scale roller bottle cultures for interferon. So there was some knowledge about that, and there was a cell line that people studied that made interferon. So we had a little bit of technology to do that, and we could get started.

We grew the tPA-producing CHO cells in these roller bottles and did pre-clinical studies in dogs and sure enough it worked.[1] We figured out what dose would be needed. Elliot Grossbard was our doctor who set up the human clinical trials across the country, and we did the safety test and the efficacy test during 1984 in humans with this roller bottle tPA[2]. When you do the math on making tPA that way, it is going to be fantastically expensive, so we had to figure out something else. One of the guys we hired was Dr. Rob Arathoon, who's now one of our VPs. He came from Burroughs Wellcome. There, they had grown BHK[3] cell tissue culture cells in

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[1]F Van de Werf, SR Bergmann, KA Fox, H de Geest, CF Hoyng, BE Sobel, D Collen, "Coronary thrombolysis with intravenously administered human tissue-type plasminogen activator produced by recombinant DNA technology," *Circulation* 69, 605-10 (1984).

[2]D Collen, EJ Topol, AJ Tiefenbrunn, HK Gold, ML Weisfeldt, BE Sobel, RC Leinbach, JA Brinker, PA Ludbrook, I Yasuda et al, "Coronary thrombolysis with recombinant human tissue-type plasminogen activator: a prospective, randomized, placebo-controlled trial," *Circulation* 70, 1012-7 (1984).

[3]Two million liters of baby hamster kidney cells were grown in suspension at Wellcome during 1983. PJ Radlett, TW Pay, AJ Garland, "The use of BHK suspension cells for the commercial production of foot and mouth disease vaccines over a twenty year period," *Dev. Biol. Stand.* 60, 163-170.

suspension on a large scale in tanks to make the hoof and mouth disease vaccine. That's kind of a coincidence. One of the largest-scale tissue culture systems in the world was the cell media for the hoof and mouth disease virus.

Rob Arathoon pointed out that instead of having giant fermenters with these propellers in the bottom stirring things up--the *E. coli* system had what was like an airplane propeller that caused the required oxygen to go all through the media so you could grow *E. coli* because they need a lot of O_2--we needed to change the gear ratio on this propeller and stir it very, very slowly. Then instead of growing the cells on the inside surface of the roller bottle, we could grow them in suspension culture. CHO cell suspension culture was Art Levinson's idea. He had adapted some of the high tPA-producing CHO cell lines for growth in suspension. So now we could put these two ideas together.

Hughes: Why did you use BHK cells?

Kleid: There are three reasons: one is amplification. There's a mutant of the CHO cell that is missing a gene called dihydropholate reductase (DHFR), which is required for it to grow. You can complement that gene with a plasmid that has the gene that encodes that DHFR gene. You put a plasmid in with the DHFR gene and select for CHO cells that have the gene incorporated. And then you can do another trick, which is to gradually increase the amount of certain chemicals--I'll just call them that--so that the cell gets a little sick. But it gets away from that by making more and more of this DHFR gene product. It starts doubling and tripling and quadrupling the copies of this gene. It's called gene amplification. It's one of the rare genes that just keeps copying and copying and copying. Art said, "We'll hook the tPA gene right next to this DHFR gene. Then, when we select for amplification for DHFR, we'll also get amplification of our tPA."

Hughes: How much of this basic science was being worked out at Genentech?

Kleid: A lot of it. One of Art Levinson's lab mates was Dr. Chris Simonsen, who came from Stanford where he had worked with a very famous scientist, Robert Schimke. They had cloned the DHFR gene and studied this amplification phenomenon, which had some implications in cancer. They made a smaller version of the gene that could be used in transfection vectors.[1] So Art and Chris used this idea, made a plasmid, and hooked these two genes together (tPA and DHFR) so that they could cause amplification to make more and more gene copies inside the cell. It takes several months to do this amplification and selection. You start out with one concentration of the chemicals and keep raising the concentration a little more and more and more and select for cells that survive and make more of your product. You gradually get the copy number of the gene to go up until the cell says, "No more. I'm making so much tPA, I'm getting sicker than I am from these chemicals." But it was a pretty good level. With the help of Rob Arathoon and his group, a new system for fermentation was designed and built so that we could grow these CHO cells in suspension and develop a process to produce clinical grade tPA

(1985).

[1]CS Gasser, CC Simonsen, JW Schilling, SR Schimke, "Expression of abbreviated mouse dihydrofolate reductase genes in cultured hamster cells," *Proc. Natl. Acad. Sci. USA* 79, 6522-6 (1982).

from 10,000-liter fermenters.[1] Nobody had ever done anything like that before. It was a completely new way of making a pharmaceutical.

Clinical Trials and the Food & Drug Administration

Kleid: Then we started the clinical trials led by Elliott Grossbard. In the clinical trials we showed that we could save people from heart attacks with this tPA.[2] One of the major problems with clinical trials is that in order to get the drug approved by the FDA one needs to have the drug proven safe and effective in lots and lots of people. Plus, the FDA wants these clinical trials blinded. So let's examine the issue. Here's somebody having a heart attack, and in the ideal world you're supposed to randomly give one person tPA and the other person a placebo, not knowing which was which. The bottles are marked just the same. If the person's heart attack continues, what do you do? Did he happen to get the placebo, or is the problem that tPA just doesn't work? Obviously no one wants to see the patient die.

So we had a protocol designed that said that after a certain amount of time if the heart attack progresses, then you would put in a catheter and use the older conventional catheter-released urokinase treatment to stop the heart attack. Comparing the data, it was possible to show that the tPA was working and the heart attack was stopping, but not with the placebo. The protocol also called for tests on the function of the heart, in particular the "ejection fraction" test. This and other tests together would show that the heart attack's gone away thanks to the tPA. So it's a tricky test. At the end of the day, everybody's happy if you can tell that the heart attack has gone away and the placebo's doing nothing. So in the end we would be saving all of the people's lives that we could from their heart attacks, but not everybody was getting tPA in the study. The study showed that tPA was working great and nobody was suffering in the placebo group.

We did this big clinical trial and then brought all the data to the FDA, asking for approval. On the same day the FDA looked at our experiment, they looked at an experiment that used streptokinase. Now, streptokinase comes from a bacterium, *Streptomyces*. Another little company that we had hardly heard of in Europe did a study in Italy where they counted bodies. They gave streptokinase or placebo to people having heart attacks and counted live versus dead bodies at the end of the test. They got two data points, dead people and live people. So the FDA said, "That data is fantastic. Look at how many lives got saved."

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[1]WR Arathoon, SE Builder, AS Lubiniecki, RD van Reis, "Process for producing biologically active plasminogen activator in recombinant CHO cells using suspension culture and removing detrimental components from medium," US Patent 5,053,334.

[2]TIMI Study Group, "The thrombolysis in myocardial infarction (TIMI) trial," *N. Engl. J. Med* 312, 932-6 (1985).

Kleid: The FDA said, "The tPA product is obviously way more sophisticated. But your data is just too complicated. How do we really know that it saves lives? The other company's data we can figure out very easily." So the FDA just about instantly approved streptokinase.

Over the next few months, we supplied more data to the FDA, and they finally said, "Yes, you're right, tPA does work," and they approved Genentech's product many months after streptokinase was approved. But Genentech's product costs \$3,000. Streptokinase costs practically nothing; I think the price is something like \$200 a shot. So here's a \$200 product and a \$3,000 product. Streptokinase wasn't even in the vision of our marketing people. They estimated how many heart attacks there are per year, and they just ran the numbers, boom, boom, boom, calculated it out: Genentech's going to be a \$2 or \$3 billion company in a matter of years. But thanks to the FDA and streptokinase, the market was immediately cut in half. Half the people are going to get the cheap stuff, and half the people are going to get the good stuff.

Then the comparisons begin and a raging argument starts that streptokinase works just as well as Activase.[1] This is even though streptokinase creates antibodies and you can only use it once. But if you have a heart attack, do you want the cheap stuff, or do you want the good stuff, the expensive stuff? The question is raised: Does tPA save more people or are [the two drugs] really just the same? So the market starts really looking sad, and more and more people are being given the streptokinase.

One of Kirk Raab's big decisions was to do a massive clinical trial where we count the bodies of streptokinase versus tPA, and see, at the end of the day, how many people live. Now, instead of having tPA against a placebo and doing this study, you're giving tPA or streptokinase and counting bodies.[2]

Hughes: Is that the GUSTO study?

Kleid: Yes. This cost a fabulous amount of money. Anybody in a clinical trial gets the drug for free. So the marketing guys, they're rolling their eyes. "You're giving this drug to all these people for free, and you're taking away all of our patients? You're doing this big study.[3] Are you really going to prove that tPA can save more lives than streptokinase?" We did the big study,

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[1]KP Rentrop, M Cohen, ST Hosat, "Thrombolytic therapy in acute myocardial infarction: review of clinical trials," *Am J. Cardiol.* 54, 29E-31E (1984); T Schreiber, "Review of clinical studies of thrombolytic agents in acute myocardial infarction," *Am J Med* 83, 20-25 (1987); KL Goa, JM Henwood, JF Stolz, MS Langley, SP Clissold, "Intravenous streptokinase. A reappraisal of its therapeutic use in acute myocardial infarction," *Drugs* 39, 693-719 (1990); GISSI-2 and The International Study Group, "In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin," *Lancet* 336, 71-75 (1990); ES Monrad, "Thrombolysis: the need for a critical review," *J. Am Coll Cardiol.* 18, 1573-8 (1991).

[2]RM Califf, et al. "One-year results from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-1) trial. GUSTO-1 Investigators," *Circulation* 94, 1233-8 (1996).

[3]In the GUSTO-1 trial, by the end of one year, 41,021 patients received one of four thrombolytic regimens. RM Califf, et al., *Circulation* 94, 1233-8 (1996).

and sure enough, the data come out showing that a couple more lives per 100 are saved with tPA.[1] With those kinds of numbers, you have to do a big study to see a difference because otherwise it's within experimental error. So you have to convince thousands of people to participate in the trial..

Hughes: Who was paying for this trial?

Kleid: Genentech.

A Clinical Partnership and Faulty Market Predictions

Hughes: Didn't one of the clinical partnerships raise money for growth hormone and tPA trials?

Kleid: Right, but the clinical partnerships were earlier. That money was used in the basic research and the early clinical trials. GUSTO was after. Fred Middleton got this idea about how to finance our work. Instead of selling more shares of Genentech outright and diluting the company shares, and instead of borrowing money, let's form a limited partnership where we sell partnership certificates or whatever, and you are part owner of a research project. At the end of the research project, if it works, we will take your partnership interest and give you shares of Genentech. I believe the deal was that each partnership unit would put in $11,000 a year for five years. In that time we raised about $50 million for the first clinical partnership concerning growth hormone and about $30 million for the tPA partnership. Then Genentech said, "At the end, if the project is successful, we'll give you so many Genentech shares for each of these limited partnership shares."

Genentech bought back the clinical partnership shares outright in 1986 before the FDA's decisions on tPA.[2] So with this calculation that Genentech was going to be a multi-billion dollar company, the shares of Genentech that were on the market went through the roof. They went from around $30 a share in 1984 to about $85-90 a share when this clinical partnership got bought out.[3] So everybody in the partnership got five times his or her money. So if you had

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[1]F Van de Werf, "Implications of the GUSTO trail for thrombolytic therapy," *Drugs* 52, 307-312 (1996).

[2]In the fourth quarter of 1986 Genentech recorded a charge of $366.6 million for acquisition of the assets of its first two limited partnerships, GCP and GCPII. These first two limited partnerships raised $55.6 and $34.0 million for the projects. The partnerships were "repurchased" for approximately 10 million Genentech shares which traded as high as $46.8 that quarter, calculated after Genentech shares were split. The recorded charge represented that portion of the purchase price that was allocated to in-process research and development projects and accordingly was charged as an expense. (This information was provided in Genentech's 1987 annual report.) Thus, the approximately $90 million invested was "repurchased" for approximately $500 million in shares.

[3]By the time the limited partnerships were purchased during late 1986, Genentech shares had split (3 for 2 in March 31, 1983 and 2 for 1 in March 3, 1986) e.g. 3 for 1, and 2 for 1 again in March 2,

Kleid: Well, the shares were now redeemable so that Roche could buy the shares back any time at a predetermined price. So the Genentech shares actually acted more like a bond because at some point in the future Roche could buy them back. Of course, the shares would always be selling somewhat below the price that Roche could buy them for. The price would not fluctuate up and down with anything Genentech or the market did; it would be totally controlled by whether Roche was going to buy the rest of Genentech or not, and each year the shares would go up about $5.[1]

Hughes: It was a stabilizing force.

Kleid: Right. The share price was down to $14 from $64 in 1987.[2] What was stopping it from going the rest of the way? Wall Street likes to see companies be profitable. We weren't going to be a billion-dollar company with just tPA and growth hormone. With the cost of making them and keeping this place open, unless we cut back and quit on research and kind of shut down, we weren't going to be profitable. So now, with this Roche deal, nobody cared whether we were profitable anymore, although for Roche's sake we were just barely in the black every single quarter from 1990 to 1995 or so.[3] From the time we had this deal, we would always be right there hitting our goals but not making so much money. We had this infusion of money, so we could build the new research facility. That was all built on Roche's nickel.

Hughes: Why did Roche want to do this?

Kleid: Well, one reason was that they saw there was some value in Genentech. As it turned out, they made a killing on that deal. We worked with them on interferon, so they were paying royalties on interferon, which were getting higher. Now they were paying the royalties but they were going into basically their own account. They valued the company by the sales, the marketing, how much we were actually bringing in. I think Genentech was probably worth just about what they paid for it at the time. I think it was $35 each for half the shares.[4] Then they could also buy some Genentech on the open market. So they could actually kind of manipulate the shares.

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[1]During the 1990s, Genentech's stock price ranged as follows, 1990: $21.7- 27.5; 1991: $20.7-36.2; 1992: $25.9-39.5; 1993: $31.2-50.5; 1994: $41.7-53.5; 1995: $44.5-53.0; 1996 $51-55; 1997: $53.2-60.2; 1998: $59.2-79.7.

[2]During the late 1980s Genentech's stock price ranged as follows, 1987: $28-64.7; 1988 1st quarter: $37.5-47.5; 1988 4th quarter: $14.4-18.2; 1989: $16-23.4.

[3]Total revenues in $millions - income per share in $s: 1988: $344 - $0.24; 1989: $400 - $0.51; 1990: $476 - ($1.05); 1991: $516 - $0.39; 1992: $544 - $0.18; 1993: $650 - $0.50; 1994: $795 - $1.04; 1995: $917 - $1.21; 1996: $968 - $0.96; 1997: $1017 - $1.02; 1998: $1151 - $1.40.

[4]Roche acquired 42.7 million shares of Genentech's stock (half of the shares) for $1,537 million and purchased 24,500 newly issued shares for $487 million, giving them 60% of the total. Genentech/Roche then issued new Genentech shares, called "redeemable common stock," for each common share. In the end, each Genentech shareholder received $18 and half of a redeemable common share for each share held. Thus, in February 1990 Roche agreed to buy 60% of a company for $2 billion that had a total market cap of $1.7 billion at the end of 1989. Ten years later, during the first quarter of 2000, Genentech's market cap stood briefly at over $60 billion.

If the shares started going down, they could buy some on the open market, and that would push them back up again. But they never needed to do that.

Roche kept this value of Genentech on their books as an asset. When you look at Hoffmann-La Roche's assets at the bottom line, there's a big chunk of Genentech sitting there. So they were able to take that asset and everything else and then borrow more money to buy more things. They ended up buying Boehringer Mannheim. It seems to me that Swiss companies are like Swiss bankers, so everything is valued as an asset that you can borrow money on. They kept borrowing, buying, and borrowing, buying. That's how Roche got to be that big; Roche is huge from doing that, see Roche Holding. So they saw it as a good deal.

Maintaining Genentech's Culture

Hughes: The *Wall Street Journal* article continues: "'The point' [of the acquisition], said Roche's Chairman Mr. Gerber, is 'to maintain the entrepreneurial spirit of Genentech, to let them have their culture. We'd be the last ones to want to kill that.'" Well, what did happen to the culture? And how did people at Genentech feel about being owned by a big pharmaceutical company?

Kleid: Roche didn't change the culture. Their other acquisition just a bit earlier was Syntex. With Syntex, they just took the products and started marketing those products, and then said goodbye everybody at Syntex. Goodbye, gone.

With Genentech, Roche felt we were working on a number of really exciting things, and they wanted to keep that spirit going, hoping that we would generate new products for their company. Part of the deal with Genentech was that Genentech wouldn't bother worrying about selling outside U.S. and Canada anymore. If they wanted, Roche would sell every single one of Genentech's products that they chose to sell outside the U.S. The cost to them would be just half of the research part. Roche would put in some money for developing the clinical part. For them it was a tremendous deal: They owned half the company; they had control over those projects that they liked, and Genentech now would be only marketing in the U.S. So that made Genentech automatically smaller. Amgen markets to the world; we only market to the U.S. and Canada.

Hughes: You felt that was an advantage?

Kleid: Roche did. Roche bought a little over 51 percent of Genentech; they really controlled everything. But they said, "We're going to keep the culture, and we'll do that by letting the Genentechers and everybody that's associated with them have half their shares. We have the opportunity to buy the whole place, but we'll see how it goes. We can choose any day just to terminate this thing and we'll take over." But they never did.

Hughes: How did it feel to work under that possibility?

Kleid: I really didn't notice it that much.

Hughes: What about other people?

Kleid: Probably the people that were most impacted were product development. Product Development is made up of little teams that organize and manage a product's progress through the development process. Now they had to keep Roche in mind, what Roche wanted to do with the products. So the Product Development teams would have a lot of interaction with Roche. But the basic research people were still totally Genentech; there was nobody from Roche to come and say what you were going to work on. On the legal side it complicated a few deals. Roche didn't let us buy other companies. We couldn't do that sort of thing. But bringing in projects and products from other companies was possible but more complex.

Hughes: Were there Roche members on the Genentech board?

Kleid: In the beginning there were two Roche members on the board. But non-Roche members dominated. So that was okay, until the second [1995], deal. The first [1990] deal was fine. It turned out to be in everybody's best interest: Roche made a lot of money on it; Genentech thrived under that scenario. The first deal had a plan that was going to expire after about five years. Now, in 1995, it came to a time when Roche had to decide: Is Roche going to buy the rest of the shares or not? The shares were "redeemable" up until that time. I think Swanson and Raab came to the conclusion that Roche was not going to redeem the rest of the shares in 1995. Genentech's shares might drop in value if Roche passed on the buy-out.[1] They were worried about their own nickel, as far as I'm concerned.

The "Put" Deal with Roche

Kleid: They went to Roche, especially Kirk Raab, and made a second [1995], deal. The second deal was that we would continue this escalation of the stock price where Roche would have an opportunity to redeem Genentech shares at a certain price that was going up and up and up. That would be fine; I think Roche would be perfectly happy with it. But Raab had a kicker that if Genentech stock went down by the end of the next five years, then we could sell our shares to Roche for $60. That was called the "put." I think the escalating price was from $60 up to $85. They could buy all the rest of the shares at any time prior to the end of this period (2000), or not. If not, then the redeemable shares would become regular common shares. But Bob and Raab were worried about the downside. What if something went wrong and we were terrible? What if Roche didn't buy the rest of the shares and they went back down in value. With this second deal (1995), we could sell our shares to Roche in 2000 for $60 if Genentech went downhill instead of up. Which was <u>stupid</u>. We didn't need to do that. Partly

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[1] I think they thought that if Roche didn't think Genentech was worth that price at that time, then neither would the stock market.

because of the "put" feature of the deal, Genentech shares floundered below the $60 number until 1998.[1]

Hughes: That was recently.[2]

Kleid: Yes, in 1999 Roche bought all the Genentech shares and then resold them to the public.[3] So the 1995 deal had the continuation of the escalation part of the 1990 deal plus the "put." Also Roche added some other conditions because it really didn't want to do this "put" thing: With this "put" thing, Roche would have to buy all the Genentech shares for $60 whether they were worth $60 or not. The Roche people said, "Well, your company's not even worth $40. Why should we agree to $60?" So they added more conditions, like how we were going to pay for the products that were being jointly developed, and how Roche would chose which ones they wanted in on; there were some changes in that way.

It turned out that just prior to the end of this five year period [1999], Genentech was doing very, very well, and our products were looking extremely good. Herceptin and Rituxan were coming out, and tPA and growth hormone had continued to do well. Genentech's product pipeline was looking really nice. Genentech was worth every bit of that $85 price Roche could buy us for. The stock market responded as well. Also, the financial analysts were saying that this buyback option that Roche had in 1999, was actually depressing the share prices; Genentech would go way higher if we didn't have this deal. Roche said, "No, I don't think so." They had two choices at that point: either buy the Genentech shares at $85 or not. Nobody was going to "put" his or her shares because we were way above that $60 "put" price. So we, quote, "beat the put." That was a big mantra of Art Levinson's. And then surprise, surprise, Roche decided to buy all the Genentech shares. I think it was Genentech people who suggested to Roche that if they were indeed going to buy the redeemable shares, they should sell some of them back to the public.

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[1]During the 1990s Genentech's stock price ranged in price as follows 1990: $21.7- 27.5; 1991: $20.7-36.2; 1992: $25.9-39.5; 1993: $31.2-50.5; 1994: $41.7-53.5; 1995: $44.5-53.0; 1996 $51-55; 1997: $53.2-60.2; 1998: $59.2-79.7.

[2]"Genentech Relaunched with Independence Intact," *Nature Biotechnology* 1999, 17:634 (July). [SSH]

[3]On June 2, 1999, Roche announced its decision to exercise its call option and acquire all outstanding Genentech shares, and this was accomplished on June 30,1999. Shortly thereafter Roche began to make these shares available to the public. As reported in Genentech 2000 Annual Report, Roche made several public offerings of Genentech's shares: 88 million on July 23, 1999, 80 million on October 26, 1999 and 34.6 million on March 29, 2000, and sold 13 million shares in exchange for zero-coupon notes on January 19, 2000. Roche's percentage ownership was approximately 58% on December 31, 2000.

Kirk Raab Resigns

Kleid: The 1995 deal, as it turned out, was not that good. It caused all the stockholders to sell their shares at $85 and pay capital gains. Roche then sold those shares back to the public in offerings that valued the stock much higher. They got all of their money back that they spent to buy Genentech, and then some. Also, while making that deal, there was incident where Raab lost his job. While he was talking to Roche about this 1995 second deal and the "put" idea, he also asked them would it would be okay if they signed off on a loan for him. He and his wife were building a house in Woodside with a fancy swimming pool and a sunken tennis court ,etc., etc, and it was just costing an absolute fortune, $10 million or something. So he asked Roche if it would be okay if they signed off on this loan for him, kind of countersigning it and guaranteeing to Raab's lender that the loan would be re-paid someday, and they said, "No." But nobody at Genentech knew anything about this.

After the second deal [1995] was signed with this "put" thing, some people said, "This is really a stupid deal," and we got a shareholders' lawsuit. The shareholders' suit caused us to collect documents and defend our position, and our little LRC crew--our Litigation Resource Center that I worked with at the time--collected all the documents for the attorneys, and they found this one document having to do with Raab asking Roche to countersign this loan. That document was given to the VPs here. They hit the roof, because that's a conflict of interest. So they told Genentech's board, and they fired Raab immediately. But who was going to replace Raab? There were three or four choices for taking over Raab's place. Roche liked Art [Levinson] the best. He was already a member of the management committee, being a VP, and the most important thing about Genentech was the research side. This of course was Art's area.

Hughes: Do you know who else was being considered?

Kleid: There weren't that many choices. One could have chosen the head of marketing, or the head of legal, or the head of manufacturing.

Hughes: Or go outside.

Kleid: Yes, they could have brought in one of their own people. That would have been the most logical thing, and that's probably the next best choice.[1] But there was something about Art's spirit, and he made a very good impression on the Roche people throughout the previous three or four years.

Hughes: Did Art go after the position?

Kleid: I don't believe so, but I don't know. He was just the kind of guy that everybody really related to. So he was a really good choice.

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[1]However, I would hate to speculate as to how well that would have gone over with Genentech's employees.

Swanson Resigns As CEO

Hughes: Speaking of relationships, what about that of Swanson and Raab? In 1990, Swanson stepped down as CEO and Raab took his place.

Kleid: That was just at the same time of the first Roche deal, in February 1990. Bob saw lots of examples where the CEO hung on too long, and it impacted the company negatively. He thought founding CEOs really needed to step aside and get out at some point. I never agreed with that. I think he would have been fine all the way through. Hewlett and Packard started in their garage, and they're still running the place, and those two were some of Bob's idols. In fact, David Packard was on our board of directors.

For some reason, Bob decided to step back from that. There may have been some tensions between him and Kirk Raab. I don't know personally, but I can imagine there were. Maybe Bob didn't want to work under the Roche deal; I don't know. But there was absolutely no indication that there was any tension shown to us who worked at Genentech. Bob and Kirk would always have big smiles on their faces. They did a lot of things together. So although there may have been problems, they kept them personal.

Hughes: Raab, of course, had come from big pharma, from Abbott. How did he react to Genentech's culture?

Kleid: He did talk about the change quite a bit: At Abbott he said it was like he was steering a giant ship and he could change its course only a little bit, but in a little company one could make a lot bigger impact. That was his view of things when he came in '85. Swanson felt that we needed more emphasis on the marketing side, and that's where Raab came from--marketing and getting drugs approved. That end of the company was the part that Bob felt the weakest in, and helpless after the FDA ended up making a mess out of our hGH and tPA projections. Growth hormone did not get approved till '85,[1] and it was supposed to get approved in '83, so that was an area that needed a lot of attention and was critical. So he brought in Raab who was experienced in marketing and getting drugs approved.

Hughes: How did Raab do?

Kleid: I thought he did fine. The GUSTO trial brought tPA back, and the growth hormone market kept getting bigger and bigger. Even with the competition with Eli Lilly, we still did very well. So the marketing arm was very well managed, and the people in marketing did a super job under that kind of management.

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[1]Then Eli Lilly was let on the market with Humatrope(TM), and Genentech's "met-less" growth hormone product was kept off the market by the FDA and their interpretation of the Orphan Drug Act.

More on tPA

Competitors

Hughes: In tPA, I know you had competitors. Genetics Institute, Biogen, and Integrated Genetics are three that I know of, and there may have been others. What happened?

Kleid: Well, GI had a project with Wellcome.

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Kleid: The GI-Wellcome project was the only competitor that mattered. The project started on their side with, of all people, Jim Watson at Cold Spring Harbor. Jim Watson decided in 1980 or 1981 that he liked the looks of all these biotech companies. They decided to form a commercial company within the sphere of Cold Spring Harbor called Cell Biology, Inc. or Corp. Jim Watson hired a CEO, a president. Of course, he's a famous moneymaker. They decided they would do tPA. Joe Sambrook was the leader of the research side of their tPA project. Now, as I told you, we had a lot of trouble cloning the gene for tPA, and so did they. It was a huge amount of work, and they spent way longer than they thought to get a clone. After a whole lot of trying, they finally got a "partial" cDNA clone that they named Sam 1, named by Joe Sambrook. It was number one and the only one. It was a piece of the tPA cDNA gene, just a chunk of it. It had taken them so long to get it.

At the same time, Genetics Institute started, with Mark Ptashne and Tom Maniatis. I mentioned to you that I used to work for those guys. At one point in late 1979 or 1980 I was on the East Coast, and I went by to visit Mark, and I gave a little seminar in his lab. Afterward he said, "I really like what Herb Boyer did with Genentech. I'm going to start a company just like he did so I can have a million dollars too." I rolled my eyes. I said, "This is a little bit harder than you think. There's a lot involved here. Basically what you're saying is you're just going to copy what we do." "Yes, I just want the million dollars. As soon as I get the million dollars I'm gone."

So he and Tom Maniatis started this company. They got a business guy, Gabriel Schmergel, I think was his name. They started Genetics Institute in just the same way as Genentech. They wanted a little lab that had some ties to Harvard, just like we had some ties to UC with Boyer. Ptashne was going to stay at Harvard Bio Labs, and Maniatis or somebody else was going to be in this company a few blocks away. They were going to get support from a big pharma company, as we had. They signed up with Baxter just like we did with Lilly. And what project do they decide to work on? tPA just like Watson! As I said, Watson and Sambrook also wanted to do tPA. Watson tells the story how he went to some place near Abbott Labs where all the urine was collected in these urinals to make urokinase. You went to the bathroom and all the urine was saved. This is a pretty smelly thing. So that's why he got interested in it. Because they had so much trouble, Watson and Sambrook decided to join forces with Ptashne and Maniatis. The "Cell Biology Company" didn't have a lot of good management and ran out of money. Watson and Sambrook really bad-mouthed the managers of their company.

Genentech v. the Wellcome Foundation and Genetics Institute, U.K.

Kleid: What happened next was, Genentech's Activase(R) product came out in 1988 and our patent issued in Europe and eventually in the U.S. The day our patent issued in England,[1] the Wellcome Foundation filed a suit to knock out our patent so they could practice the invention. By this time, GI and Cell Biology had joined their projects together, and they joined up with Baxter-Travenol. Baxter-Travenol eventually lost interest in the project because Genentech had published its work and filed for patents before GI-Cell Biology even cloned the gene. So they sold the whole project to Burroughs-Wellcome.

Now Burroughs-Wellcome in England was trying to scale up the tPA process that had been developed using the cells created by GI. The GI tPA process ended up using tissue culture cells like Genentech's product, and growing these cells in tanks.[2] Our process uses serum-free media. It starts with a low concentration of fetal bovine serum, but then there's a step where all the serum is removed, and the last fermentation is actually in serum-free media. We purify out of serum-free media, whereas they purified it out of serum-containing media. They developed a process that uses antibodies to absorb out the tPA, and they end up with stuff that's not a very clean product in my view. They went into clinical trials with their product in 1987 while we were waiting for approval for our tPA. The data on our stuff was looking really good, curing all these heart attacks, and their stuff was causing people to bleed unexpectedly. It was just terrible, especially since streptokinase was also being used at that time. Some of the same study centers that were testing Wellcome's tPA had previously tested Genentech's tPA. The data from their studies might screw up approval of our tPA. So we were getting concerned about that.

One of the marketing guys said, "Maybe we should get a sample of their tPA to see what's going on." One sales rep got a tiny 10 mg vial of Wellcome's tPA from a nurse working with Wellcome's tPA clinical trial. He also gave her $100. At Genentech, we did all these tests on it, and showed that it's got contaminants in it. That later becomes a huge issue during the patent litigation in the U.S.

Let's go back to the Wellcome suit in England. The basic premise of Wellcome's case against our British tPA patent was that our invention of making tPA from the cloned cDNA--the Dave Goeddel and Diane Pennica et al. invention (I told you how difficult it was)--was obvious; anybody could do that. Wellcome: "We did it after you, but we used all the same methods you did. We had a plan, and it just worked like clockwork, boom, boom, boom."

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[1]GB 2119804 DV Goeddel, WJ Kohr, D Pennica, GA Vehar, "Human tissue plasminogen activator pharmaceutical compositions containing it, processes for making it, and DNA and transformed cell intermediates therefor," (application filed May 5, 1982 and published November 23, 1983).

[2]RJ Kaufman, LC Wasley, AJ Spiliotes, SD Gossels, SA Latgt, GR Larson, RM Kay, "Coamplification and coexpression of human tissue-type plasminogen activator and murine dihydrofolate reductase sequences in Chinese hamster ovary cells," *Mol. Cell Biol.* 5, 1750-9 (1985).

Wellcome had Tom Maniatis as a spokesman saying, "I could do this with my eyes closed. Joe Sambrook and I, we had no trouble. This is obvious. Anybody could do this."

One of the big problems with the case was that Wellcome wanted to find out how Genentech actually makes its tPA, so they asked us for all of our documents on our big-scale process. Here you are in litigation with these guys, and they're going to take these documents to England, and who knows what's going to happen? All our secrets are going to be gone. So we limited the case and made a deal with them saying, "Look, the process part has nothing to do with the invention, so you don't need those documents. The invention was getting the gene for tPA." With that stipulation we went to trial.

The judge in the end agreed with Wellcome and said anybody could do it; there were no new tools developed to clone the tPA gene. The British patent system is pretty weird. You have to make two inventions, I guess. One is getting the tPA gene. Another is inventing a new tool to get there. Only then is it not obvious. But if you're using existing tools, it's not an invention; it's like finding something; it just takes time. You don't get a patent for carrying out something that is difficult. So the British judge said that anybody could get a tPA gene at that time if they had a good organization and money to pay for the project.

We appealed that decision. It went to a tribunal of members from the House of Lords. The tribunal said, "Well, the judge wasn't exactly right. It was beyond ordinary skill to make the tPA gene. Ordinary skilled people could not have done this." But they said, "Although Genentech discovered the tPA sequence, discoveries aren't patentable here; only inventions are patentable in England. Since the use of that tPA gene to make tPA was obvious (because Genentech had stipulated to that), all you made was a discovery."[1] So good-by to Genentech's British patent. In the U.S., the law says inventions or discoveries are patentable as long as you also provide a utility for that discovery. We lost our patent in England, and since then the world has repudiated that decision. Everywhere else in the world, our tPA patents are good.

Genentech v. Wellcome, U.S..

Kleid: Wellcome then said, "Now we've got to knock out Genentech's patents in the U.S." So they filed a Declaratory Judgment Action and tried to do the same thing in the U.S, in Delaware. But in the U.S. the patent laws are different; Wellcome couldn't make the same arguments. In the U.S. they basically made two arguments. One was that they didn't infringe our tPA gene sequence patents because they had a mistake in their gene. One amino acid was different due to a cloning error. The Delaware judge found that Wellcome's tPA was not "human," and so Genentech had to prove that the products were "equivalent."

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[1]This would be analogous to discovering a comet. Halley named the comet after himself, but that is not an invention, and he can't get a patent on it. Of course comets don't have any real world use. The tPA gene certainly did--but that was deemed not to be part of the "invention."

The second issue was that they accused us of inequitable conduct: They said we got the patent by telling the patent examiner that the tPA messenger RNA concentration was very low, and it really wasn't low. So we lied to the patent office. And also they brought out a tiny little box with a 10 mg bottle of Wellcome's tPA in it, similar to one that ended up being tested at Genentech. Wellcome told the jury, "Genentech paid a nurse $100 to get this bottle from the clinical trials, and somebody could have died." They went on and on explaining all of these bad deeds and tried to get the jury to knock out the patent for inequitable conduct. I was at that trial. It was horrendous. At the end, the jury said, "No." They let us keep our patent, and every single juror was on our side. They took less than a couple of hours to decide. The Wellcome challenge of our patent didn't work. Now we had the U.S. patent, and we enjoined them from making, using, or selling tPA in the U.S. That's the end of GI's, Cell Biology's, Baxter's, and Wellcome's tPA program. It's gone! We wiped it out![1]

Scale-up

Hughes: An article in *Science* published in 1987 stated that at that point only Genentech and Wellcome had the technical know-how and facilities to grow mammalian cells in large volume.[2]

Kleid: That's right. Remember, I said that we brought Rob Arathoon to Genentech. Where did he work before? Wellcome. He ended up hiring a couple of his friends from Wellcome. This was another issue that Wellcome's attorney brought up at the Delaware trial. The jury found, however, that we did not impede Wellcome's progress by hiring away a couple of their people nor did we copy their process.

Hughes: You mentioned the huge fermentation system, but I'm surmising that there must have been technical problems connected with moving with a very complicated molecule from the bench to huge volume.

Kleid: The next step after you grow the cells up in these giant tanks is to purify the tPA from the media and put it into vials with a stable formulation. The leader on that process was Stuart Builder. He had some really good people working for him. John Ogez is one name that comes to mind.[3] They developed a process on the bench that was scalable to bigger tanks. One of the

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[1]Genetics Institute had another tPA-like molecule called "FE1X" that was also the subject matter of the Delaware trial. This material had a large deletion that removed important parts of the tPA protein. Its activity was more like streptokinase than tPA. Although the same Delaware jury found that this product was equivalent to the human tPA claimed by Genentech, that decision was reversed on appeal. *Genentech Inc. v. The Wellcome Foundation Ltd.* 31 USPQ2d 1161, 29 F.3d 1555 (Fed. Cir. 1994).

[2]Marjorie Sun, "Companies Vie over New Heart Drug," *Science* 1987, 237:120-22. [SSH]

[3]JR Ogez and SE Builder, "Downstream processing of proteins from mammalian cells," *Bioprocess Technol.* 10, 393-416 (1990). WF Bennett, SE Builder, LA Gatlin, "Stabilized human tissue plasminogen activator compositions," U.S. Patent 4,777,043, and VR Anicetti, SE Builder, BJ Marks, JR

keys was growing the cells in serum-free media. The major protein in the media was tPA. The next important step in the process used lysine-Sepharose.[1] tPA likes to bind to the lysine. So they developed a process using lysine-Sepharose columns. The media was poured through there and then eluted. That's called affinity chromatography. Wellcome used antibodies to do that step. They started with the serum-containing media . So they had a lot more downstream steps than we did.

Clinical Trials and Criticism

Hughes: Talk about the relationship between Genentech, Elliot Grossbard, and the cardiologists who were testing tPA in the clinic.

Kleid: Genentech and Elliot, with the help of several major cardiologists in the United States, developed the original tPA clinical trial protocol that we already talked about, where they tested tPA in people and designed the protocol that incorporated the urokinase treatment if the heart attack progressed. Elliot then went to different hospitals that dealt with heart attacks and set up clinical studies there. He managed the cardiologists so that they could do the study, and then they collected the data for us to use in our submission to the FDA.[2]

We have here at Genentech clinical research associates. These are basically nurses; my wife used to be one. She worked on the cancer side of things. They would go to the centers where the tests were going on and collect case report forms. Each person who took the tPA would have a report on how much they got, when they got it, what the results were. Then they had the statisticians here figure out what was happening as far as the whole group was concerned, so that they could then take all the data and give it to the FDA. It's not really anything unusual.

Hughes: I remember reading some criticism.[3]

Kleid: I think you are recalling issues that arouse later in the mid 1990s, after the GUSTO trial. Some of the doctors had previously gotten involved with issues concerning being paid consultants or buying shares of companies that were sponsors of the trial, and that was dealt with right at the

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Ogez, EJ Patzer, DA Vetterlein, "Method of purifying recombinant proteins from corresponding host cell proteins," U.S. Patent 5,411,864.

[1]Radcliffe et al., *Arch. of Biochem. & Biophy.* 189, 185 (1978).

[2]EB Grossbard,, "Recombinant tissue plasminogen activator: a brief review," *Pharm Res* 4, 375-8 (1987).

[3]Ralph T. King, Jr., "FDA Widens Probe of Genentech," *Wall Street Journal*, November 10, 1994, p. A3. [SSH]

beginning of the GUSTO trial.[1] The doctors decided they would not take any consulting money from the companies that sponsored and funded the tPA and streptokinase GUSTO trials.

Hughes: That was one criticism.

Kleid: I don't know how that came about. The idea was that they might be skewing the data. But that was pretty much impossible because the way the study was designed you didn't know which patient was getting tPA or streptokinase.

Hughes: They were accused of skewing the data?

Kleid: No, there was never any accusation like that. There was a perceived conflict of interest. That was the sum of it. We just don't let doctors buy shares of Genentech when they are working on our studies.

Hughes: It does seem like a conflict of interest.

Kleid: It can be. Especially if a small company needs this one study done, and the doctors are part of the company. There were examples of that.[2] Genentech's study was pretty separated from the company itself. There's no question that Elliot worked for Genentech. He was not doing any studies at all; he was just getting the cardiologists signed up and collecting the data.

In the marketplace, there were more issues with the competition between streptokinase and tPA. Here you'd got the "cheap stuff" streptokinase and then you've got the "Cadillac stuff" tPA and the results of the GUSTO trial. What does that mean?[3] So how do you market them? It was pretty complicated. I didn't know anything about how our sales reps dealt with cardiologists and this dichotomy between the costs of the two products.

Marketing tPA

Hughes: Another accusation was that Genentech used some aggressive advertising for tPA. Ads came out in some of the medical journals before FDA approval. There was a marketing campaign to make tPA a very visible drug to cardiologists, the physicians who would be prescribing it, of course.

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[1]EJ Topol et al., "Confronting the issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion GUSTO Steering Committee," *J. Am Coll. Cardiol.* 19, 1123-8 (1992)

[2]All I can recall is a made-for-TV movie with a plot along those lines.

[3]RM Califf, D Stump, EJ Topol, DB Mark, "Economic and cost-effectiveness in evaluating the value of cardiovascular therapies. The impact of the cost-effectiveness study of GUSTO-1 on decision making with regard to fibrinolytic therapy," *Am. Heart. J.* 137, S90-3 (1999).

Kleid: I think that's traditional in that time period, 1980s-1990s. They had alerted the cardiologists that tPA would someday be approved. The test data was published along the way, prior to approval. But, I certainly don't believe anyone was allowed to market an unapproved prescription drug to the patient. I don't really see an issue about alerting physicians in medical journals to tPA before approval. Putting information in the medical journals was the only way physicians would know about tPA. The drug was actually sold by our distributors. It goes directly to the hospital. It's not sold to the cardiologists. So the sales reps went to visit the cardiologists to tell them about tPA. They didn't actually sell them anything; they just gave them information. That's the way you market something like that.

There was no such thing as thrombolytic therapy before tPA and streptokinase. It was an entirely new way of treating heart attack. Before, you got your heart attack, and the doctor wrung his hands and said, "Oh, God, I hope you make it," and your heart was damaged for life. Now with this new treatment you were actually going to be doing some intervention. So the doctors needed some encouragement to do something.

The story with tPA for stroke is really amazing. As you may know, we developed tPA for stroke and supported clinical trials for that.[1] Cardiologists were used to coming in for emergencies, getting the hearts going again, or doing bypass operations. Whereas neurologists who deal with strokes were used to prescribing physical therapy--after the fact. They never had training for "stoke emergencies" because there was no treatment for that anyway. In order to successfully use tPA for stroke, the patient needs to be treated within a few hours. We had a horrible time trying to convince them that there was a new treatment out there and don't just wring your hands. Stroke treatment with tPA must be done very soon, because if the clot sits there too long it damages the brain vessels, and then tPA can cause bleeding when it resolves the clot. In order to get acceptance and higher use of that new stroke treatment, you've got to put the sales reps out there to tell the neurologists about it; it's the only way.[2]

Hughes: What I thought was the source of the criticism was the fact that Genentech placed full-page ads about tPA in medical journals before the FDA had approved the drug.

Kleid: I remember there was one ad--it was either for tPA or growth hormone--where it said, "Coming soon." I don't know if that is the one you are referring too. Preapproval tPA ads would have been in 1987 when the streptokinase-tPA tension was pretty difficult to deal with. In '87, I was involved with the Wellcome trial, which sucked up all of my time, so I don't really know about that.

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[1]National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. "Tissue plasminogen activator for acute ischemic stroke." N Engl. J. Med. 333, 1581-7 (1995)

[2]JL Saver, CS Kidwell, S Starkman, "Commentary: Thrombolysis in stroke: it works!" *BMJ* 324, 727-9 (2002), J Lenzer, "Alteplase for stroke: money and optimistic claims buttress the 'brain attack' campaign," *BMJ* 324, 723-9 (2002).

Hughes: The picture you're painting shows Genentech scaling up for a big drug expected to have huge revenues. How much did Kirk Raab have to do with this orchestrated approach to marketing tPA?

Kleid: Well probably quite a bit, although again, I was not in the loop. We called it "the launch." Genentech planned it for many months. All your teaching materials [were ready] and sales reps were trained to understand what they were going to be selling. There were all kinds of new hires. They were there for months ahead of time so that when we were ready to ship the drug they could go out and interest people in buying it. If you just ship a drug and nobody knows about it, nobody's going to buy it. There are a lot of people to talk to in hospital pharmacies; it has to be there. Then the cardiologists have to order it, and then the public has to know that there is the opportunity.

Hughes: How was the initial connection with the cardiologists made?

Kleid: It was mostly with the ones that did the studies. We did a lot of studies; we had all the major medical centers involved. The cardiologists were extremely excited about how tPA would work, and there were lots of publications.[1]

tPA and Angioplasty

Kleid: The other competing process was angioplasty. These two treatments kind of fit together, because if there's a heart attack you've got to get the blood flowing right away, and tPA would get things going. Then the next day, or maybe later that same day, you do the angioplasty to make the artery wider.[2] Nowadays, the competition is with the stents, these tiny wire tubes that you put in at the narrowing of the artery that hold the blood vessel open.[3] My dad has one. They are really knocking down thrombolytic therapy. They can do that pretty fast, and they're about the same price, and then you don't need to bother with the tPA.

Hughes: What's happening currently to tPA sales?

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[1]M Versraete, AE Arnold, RW Brower, D Collen, DP deBono, C deZwaan, R Erbel, WS Hillis, RJ Lennane, J Lubsen et al., "Acute coronary thrombolysis with recombinant human tissue-type plasminogen activator: initial patency and influence of maintained infusion on reoccusion rate," *Am J. Cardiol.* 60, 231-7 (1987).

[2]DO Williams, NA Ruocco, S Forman, "Coronary angioplasty after recombinant tissue-type plasminogen activator in acute myocardial infarction: a report from the Thrombolysis in Myocardial Infarction (TIMI) Trial," *J. Am Coll. Cardiol.* 10, 5 Suppl B, 45B-50B (1987).

[3]A Colombo et al., "Coronary stenting in 1000 consecutive patients. Long-term clinical and angiographic results," *G. Ital. Cardiol.* 27, 19-31 (1997).

Kleid: They've been dropping for quite a few years. So we have come up with a better and more improved tPA. It's called Tenecteplase.[1] Scientist here at Genentech figured out how to make a tPA that will work faster, can be used as a single shot rather than an infusion, and is slightly safer.[2] By changing a few amino acids here and there, they've come up with a genetically engineered design. Instead of having God design it, they'll change a few things and make it better. Now Tenecteplase is sold for heart attacks. tPA is still used for strokes.[3] tPA has also been approved for another problem that people have. Dialysis lines get clogged with blood clots. You add tPA to keep the dialysis running.[4] Although the sales are not going up, there are beginning to be more uses.

Genentech Strategies and Policies

Rewarding Employees with Share Options

Hughes: I read that when drugs such as human growth hormone and tPA were approved, Swanson, and I guess Raab, granted each employee an option to buy a hundred shares.

Kleid: Yes, I remember that. I think we might have done that one time or maybe two. That was fun! At most companies, every year or two--

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Kleid: --you have a chance to be awarded options to buy shares at a predetermined price. Usually the option price is near where the shares are currently trading. You're given an option, and you hope down the road that the price of the company will go up. But these options don't vest immediately. You have to stay at the company for a year and then over the next three years

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[1]L McGahan, "Tenecteplase: single-bolus thrombolytic therapy for acute myocardial infarction," *Issues Emerg Health Technol.* 2001, 1-6 (2001).

[2]BA Keyt, NF Paoni, CJ Refino, L Berleau, H Nguyen, A Chow, J Lai, L Pena, C Pater, J Ogez T Etcheverry, D Botstein, WF Bennett, "A faster-acting and more potent form of tissue plasminogen activator," *Proc. Natl. Acad. Sci. USA* 91, 3670-4 (1994).

[3]National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, "Tissue plasminogen activator for acute ischemic stroke," *N Engl. J. Med.* 333, 1581-7 (1995).

[4]Cathflo(TM) Activase(R), see: D Ponec, D Irwin, WD Haire, PA Hill, X Li, ER McCluskey, "Recombinant Tissue Plasminogen Activator (Alteplase) for Restoration of Flow in Occluded Central Venous Access Devices: A Double-Blind Placebo-Controlled Trial—The Cardiovascular Thrombolytic to Open Occluded Lines (COOL) Efficacy Trial," *Journal of Vascular and Interventional Radiology* 12:951-955 (2001); H Eyrich, T Walton, EJ Macon, A Howe, "Alteplase versus urokinase in restoring blood flow in hemodialysis-catheter thrombosis," *Am J. Health Syst Pharm* 59, 1437-40 (2002).

more and more of the shares will vest. Anytime after they've vested, you can buy the shares at that option price. Then you can sell them for whatever price they are at that time--or later. It has a tendency to keep employees around longer and make them a bit more dedicated than you would get with a paycheck and a time clock. You look at that downstream and you say, "Wow, if Genentech does really well then I should stay here." Most companies, before Genentech, only did things like that for the management. But here, it's up and down the company; all the exempt employees have that.

Hughes: Is that one reflection of Genentech's culture?

Kleid: Oh, absolutely. It was one of the first to get interested in the stock market, because our president came from the venture capital area, so Bob instilled in all of us building value in the company, not just making profits. We've never really talked much about profits; we would always talk about building value in the company.

Hughes: Although I am very aware that Herb Boyer was in the wings, there weren't too many early biotech companies that had a business person heading them. And if there was a business person as president, there were often scientists with a lot of prestige breathing down his neck.

Kleid: I can certainly see the contrast with almost every other biotech company. As I said, Ptashne, said, "I want to be a millionaire, so I want to start this company." Then he hired a CEO. His idea was to copy the Genentech concept. Most of the companies started with one idea. "We have an idea to make this product," and that idea normally came from the scientists, naturally. So the company would be devoted to developing that idea into a product. Whereas Swanson said, "I want to create a fully integrated pharmaceutical company. The scientists will make this happen." Although the first project was human insulin, it was only the beginning. We were not going to be a one-idea company.

Becoming a Fully Integrated Pharmaceutical Company

Hughes: Was Genentech a FIPCO--fully integrated pharmaceutical company--in 1985 when Raab arrived?

Kleid: Well, growth hormone got approved in October '85. We had sales and marketing. I think the sales reps were trained for two years before '85. Bob Byrnes, a marketing guy, one of our earliest vice presidents, was one of the first fifty employees. He hired Jim Gower who really did the growth hormone launch. Jim Gower was the head of marketing and the one that put together our first real marketing group. That's one part of the fully integrated company. Another part is the manufacturing side. Bill Young headed that. He came from Eli Lilly. I think the only thing we were missing for a while was filling and vialing (putting our product in the bottle and boxing it up). We had that done at another company. It might have been Lederle in the early days; I'm not sure. Then we eventually added that too.[1] So in 1985 we had basic

[1]Genentech's sterile fill-and-finish facilities were built during 1988.

research, pre-clinical research, clinical research, process development, manufacturing, and sales and marketing, as well as a regulatory group and quality control.

Hughes: By 1985?

Kleid: By the end of 1985 we had everything, except for the filing and vialing, and soon thereafter we had that here as well.

Hughes: So you didn't need Raab to turn the company into a FIPCO. It was already one?

Kleid: Well, sure, I would say so. I think Bob wanted more impact in the clinical and marketing area going forward. But for the goal to get our first product on the market, he led the whole thing.

More on the Roche Acquisition

Hughes: Anything more on Raab or Levinson?

Kleid: In 1999, at the end of the second Roche deal, Roche bought all the rest of the shares, and then sold half of them back in one of the largest IPO's ever. Roche bought the shares at $85 or so, and then they turned around and sold them for $100. Then the stock went through the moon, kept going and going. It has split twice since then.[1] So they did more public offerings and sold all the rest that they had bought and made a ton of money.[2] If you add up how much money Roche has spent on Genentech and how much they've gotten back, they got Genentech for free plus some. The worst part about this "put" thing is, when they bought all the rest of the Genentech shares, they also added more board members from Roche and kicked out all of the old ones, except for Art Levinson and Herb Boyer. So now the board is controlled by Roche, even though they don't own any more of the company than they did before.

Patent Litigations

Hughes: How do people at Genentech feel about that?

Kleid: Believe it or not, Roche has not had that big of an impact--except on one of my projects. One of my projects was a tPA patent case against Boehringer-Mannheim. Today we have one

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[1]Genentech stock split 2 for 1 on November 3, 1999 and 2 for 1 again October 25, 2000; thus in total one Genentech share from the IPO is now twenty-four.

[2]As reported in the Genentech 2000 Annual Report, Roche made several public offerings of 88 million shares on July 23, 1999, 80 million shares on October 26, 1999, and 34.6 million shares on March 29, 2000, and sold 13 million shares in exchange for zero-coupon notes on January 19, 2000.

competitor in the tPA area and it's Centocor which sells a product called Retavase(TM) or reteplase that got FDA approval in 1996. That product was developed by Boehringer-Mannheim in Germany and is made in *E. coli.*[1] Reteplase is tPA with a chunk cut off, so it's about as good as streptokinase.[2] We had patent claims direct to that type of knock-off product. Roche bought Boehringer-Mannheim, and then they were told by the FTC [Federal Trade Commission] that they had to sell the rights to the reteplase product to someone else, because Roche, in buying Boehringer-Mannheim, would be controlling two products for the same U.S. market. So Roche sold Retavase(TM) to Centocor for the U.S. market, but Roche kept the product for the rest of the world. So outside the U.S., Roche competes with Boehringer-Ingelheim (BI makes and sells Genentech's Activase and Tenecteplase outside the U.S.), and inside the U.S. Genentech competes with Centocor's Retevase.

We were in patent battles with Boehringer-Mannheim over this Retevase product in the U.S. and in Europe. After this deal was inked and settled, Genentech sued Centocor in San Francisco because we got a new patent issued [which went] beyond the patents that were being litigated against Boehringer-Mannheim. The claims in the new case were written exactly for these Boehringer-Mannheim/Centocor copy cats. Unfortunately Centocor's deal with Roche included an agreement that Roche would pay for all of Centocor's legal bills against Genentech.

We also had a patent battle in Europe. Our European tPA patent (as opposed to the British tPA patent) was pretty strong. So with this turn of events we had a patent battle to keep Roche's reteplase product off the market. I was really excited about this because it was my baby. But, in 1999 when Roche exercised its option and bought the redeemable shares, it also put their people on Genentech's board. One of the very first acts made by that board was to tell Genentech to cancel the suit against Centocor in the U.S. and withdraw the European patents on our tPA. So all the work I'd done on those litigations instantly went for naught. Now here in the U.S. we have a competitor in our market, and we get no royalties from them at all, and they have a sweetheart deal with Roche. So my work might have been impacted more than anyone else's at Genentech.

Kleid's Transition to the Legal Department As Patent Agent

Hughes: Remind me why you moved to the legal department in 1985.

Kleid: It mostly happened because the company decided they didn't want to do vaccines anymore. My area was in vaccines, and we had developed a part of the company called Vaccine Development. We hired Jack Obijeski to be the head of our little department. We were working

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[1]U Kohnert et al, "Biochemical properties of the kringle 2 and protease domains are maintained in the refolded t-PA deletion variant BM 06.022," *Protein Eng* 5, 93-100 (1992).

[2]RAPID I, Reteplase Angiographic Phase II International Dose Finding Studies," *Circulation* 91, 2725-32 (1995); JR Hampton, "Mega-trials and equivalence trials: experience from the INJECT study," *Eur Heart J.* 17 Suppl. E, 28-34 (1996).

on vaccines for hepatitis, influenza, rabies, hoof and mouth disease, herpes, and a little bit on AIDS. Originally, back in 1979 when I started in this area, Bob Swanson told me, "I think vaccines are a very bad business. But sometimes there's an opportunity where other people don't see one, so I think we should do something in that area." We started with the hepatitis project in 1980. I think we talked about this.

Hughes: Yes, we did.

Kleid: So in 1985, Bob said, "I thought you were going to do one vaccine project, and you've got all these projects, and they're diluting Genentech's efforts. We've got to get growth hormone approved." You see the problem: we were sitting there in '85 and growth hormone was not approved yet, and Genentech's board was wondering, I guess, whether Genentech was ever going to get anything approved. With those pressures, Bob decided, "We have to focus more; let's get rid of the vaccine projects." What do I have to do with growth hormone at that time? Nada! The company was just twiddling its thumbs waiting for the FDA to approve it. I guess he thought making us stop our work on vaccines would help in that "twiddling" effort. At any rate, Bob and Dave Martin said, "No more vaccines. We're taking all of your people, and we're moving them all to different labs."

Dave Martin orchestrated this. As you know, Genentech has a sabbatical leave program. After you've been here for seven years you can take six weeks off and do anything you want. So the summer of '85 I took my six weeks sabbatical, but I also had six weeks of vacation coming, so I took three months off. During that three-month period, Dave Martin transferred all the people to other places, so when I came back there was no department. He said, "We should have a program on bones. Why don't you go learn about bones?" I said, "No, we are tops in the world in this vaccine area; I'm not going to work on bones. I would rather work with the legal department." I think I told you I was working on the patent side of things from the beginning, helping out a little bit here and there. I studied for and passed the patent bar in 198, and worked half time in legal in 1985. When the tPA and the Lilly lawsuits got going in 1986 I became full time in legal. There was so much work to do helping the attorneys figure out what our evidence was, and producing the documents, and that has continued ever since.

Hughes: Do you like the work?

Kleid: It's fine. It's all right. I described it before: you have a patent; the other side wants a license; often we can make a deal to license a patent that covers what we would like to do, or make a deal to license out our patent that covers what others would like to do. At times there are problems where we can't make a deal. Usually that happens when the other side thinks that their invention is the greatest thing since sliced bread. There can be no deal when the patent owner values his patent too high. This usually happens with the other side's patents, not Genentech's--it's always the other side. Most of these cases begin because the other side is trying to get money out of Genentech, not because they made a contribution to our product. I'd say in 80 percent of our lawsuits, we're the defendants. Often what happens in litigation over patents is: (1) a product comes out that has a big market, and suddenly there is a huge amount of money on the table, (2) everyone that did anything remotely related to our product wants a cut, and a feeding frenzy for patent litigators begins. [tape interruption]

Factor VIII

Gordon Vehar and Richard Lawn: Cloning and Expressing the Gene

Hughes: Another product of these mid-1980 years was factor VIII. In April 1984 Gordon Vehar and Richard Lawn announced the cloning of factor VIII. Perhaps you could tell me how that project developed.

Kleid: That was on our original list of human proteins that we might want to do. But factor VIII had a problem--it is a huge molecule.

Hughes: Bigger than tPA?

Kleid: Yes, it's four times as big. It's more than a couple thousand amino acids long.

Hughes: Nobody knew that at the time you put it on the list?

Kleid: Everybody knew that it was very complicated and would be very difficult and very rare. It's the next order of magnitude more difficult than tPA.

The Hemophilia Foundation is a very active group. I remember one day a hemophiliac came to Genentech and gave a little talk to us about how important factor VIII is and how expensive and difficult it was for hemophiliacs to obtain factor VIII. He urged us to try to do something about this. I think he convinced us all that this would be a great project. I don't know if it was Rick Harkins or Gordon Vehar who got this project started here at Genentech. We first started by trying to purify factor VIII so that we could get some amino acid sequence data in order to clone it. Gordon came from a lab that was working on the characterization of factor VIII. Dick Lawn was a molecular biologist.[1]

So Dick Lawn and Gordon Vehar joined forces at Genentech and worked together on cloning the factor VIII DNA sequence. It's extremely difficult to make a cDNA that long, and they eventually just couldn't do cDNA cloning. If I recall correctly, they first cloned a small fragment of DNA from the genome of a human cell line that had several copies of the X chromosome. They made libraries of DNA clones and found one that had part of the factor VIII gene. The gene for factor VIII had all these introns in it, so it was just gigantic. They eventually got some chunks of the gene cloned, and out of that they made DNA probes based on the sequence at the end of the cloned DNA to find the next sequence downstream. They called it "gene walking." They were eventually able to piece together a cDNA that contained the whole gene. In 1984 it was hooked up for expression in *E. coli*. Of course nothing was going to happen in *E. coli*. So then we went to tissue culture cells, and used the same kind of system that's for tPA and hepatitis. From this they were able to make the tiniest, tiniest bit.

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[1]Coincidentally, Dick was one of the first graduate students of my former fellow Harvard postdoc, Tom Maniatis, who was then at Caltech.

Factor VIII doesn't like to get made in Chinese hamster ovary cells; it hates them. So they tried other cell types and eventually developed a method to make factor VIII using BHK cells, baby hamster kidney cells. The sequence of the human factor VIII gene, the expression of the factor VIII in genetically engineered cells, and the structure of the factor VIII protein were described in three back-to-back publications in *Nature* in 1984.[1] The team's factor VIII invention was eventually awarded "Distinguished Invention of the Year" by the Intellectual Property Owners Association.[2] For commercial production of factor VIII a new promoter system was needed because the promoter that we had used for tPA just didn't make it. So the team developed another promoter. Eventually, after struggling, they managed to develop a cell that would make a enough of the material to be commercially viable.

Collaborating with Bayer, Cutter, Miles

Kleid: Then we started working with Bayer. The Bayer Corporation of Germany had bought Cutter Laboratories in Berkeley which made factor VIII from blood. They made some of the original polio vaccine. It was a killed virus vaccine. The very first batches had a big problem because some of the vaccine still had live virus in it, and it gave polio to a lot of the first kids to take it. Unfortunately, many of those kids were the children of doctors and heath care workers. I believe it was at this time that the company sort of went into the dumpster, and Bayer bought them. Then Cutter/Bayer developed the factor VIII process to purify the material from blood. When AIDS virus first showed itself, Cutter/Bayer didn't know that the AIDS virus was present in the factor VIII that they made. Factor VIII contaminated with AIDS virus gave AIDS to many, many hemophiliacs. It was at this time that they really needed Genentech big time.

Hughes: Was the AIDS epidemic a factor in boosting Genentech's interest in factor VIII? Recombinant factor VIII could provide an uncontaminated source.

Kleid: Our interest was already there, but now Cutter/Bayer was interested.

The problem was that all the hemophiliacs were dying fast. At one time the marketing people thought that the number of hemophiliacs was going so low that there was not going to be a market for factor VIII. But much hemophilia is not passed through mother to son. Since the

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[1]J Gitschier, WI Wood, TM Goralka, KL Wion, EY Chen, DH Eaton, GA Vehar, DJ Capon, RM Lawn, "Characterization of the human factor VIII gene," *Nature* 312, 326-330 (1984); WI Wood, DJ Capon, CC Simonsen, DL Eaton, J Gitschier, B Keyt, PH Seeburg, DH Smith, P Hollingshead,KL Wion, E Delwart, EGD Tuddenham, GA Vehar, RM Lawn, "Expression of active human factor VIII from recombinant DNA clones," *Nature* 312 330-337 (1984); GA Vehar, BKeyt, D Eaton, H Rodriguez, DP O'Brien, F Rotblat, H Oppermann, R Keck, WI Wood, RN Harkins, EGD Tuddenham, RM Lawn, DJ Capon, "Structure of human factor VIII," *Nature* 312, 337-342 (1984).

[2]DJ Capon, RM Lawn, AD Levinson, GA Vehar and WI Wood, "Preparation of functional human factor VIII in mammalian cells using methotrexate based selection," U.S. Patent 4,965,199, issued October 23, 1990, and "Functional human Factor VIII," U.S. Patent 5,618,789, issued April 8, 1997.

gene is so big and complicated, a lot of hemophilia cases are the result of spontaneous mutations. Probably only about two-thirds of the hemophiliacs have a parent with the bad gene. So there are always a growing number of hemophiliacs out there.

Genentech developed the cells that make factor VIII and the first workable process for isolating the protein from those cells. Then we joined with Cutter/Bayer and developed a commercial process for factor VIII during 1985-6. We had a lot of interaction with them during the period when the process was used to make clinical material.

Hughes: This process was more productive than the one that Genentech had originally come up with?

Kleid: I actually don't know if further productivity was gained by Cutter/Bayer, the main issue was making pure material from this new source. That was successful. It's a very difficult product to make. Factor VIII derived from blood still competes very nicely. Since then Bayer developed heat treatments and other kinds of things to keep the AIDS virus out. Factor VIII from blood and recombinant factor VIII are both still on the market today. Up until this year, Bayer and Baxter Travenol--I guess Travenol's not even in the name--were the companies that made and sold factor VIII. But they had never been able to make enough to satisfy the whole market. A lot of hemophiliacs would like to have factor VIII all the time. If they could take a shot every day like insulin then they would always be protected. But because it's so expensive and so hard to get and limited in supply, they just use it for bleeding episodes.

Genentech v. Genetics Institute

Kleid: Genentech was the first to clone factor VIII, as you read, but we were the second to file a patent on it. The Baxter product came from research at GI. Co-incidentally, Tom Maniatis and Jay Toole were the leaders of the factor VIII project at GI. When they first had the idea of making a clone of factor VIII, they got a little chunk of porcine factor VIII genomic DNA and said, "Oh, we know how to do it." So after they cloned a fragment of porcine factor VIII DNA, they wrote what is generally called a "paper patent" based on paper plan for getting the full-length human factor VIII DNA. Of course, Genentech didn't file its patent until we got the whole gene and got it to work--which was a bit later.

As time went on, the patent office issued the patent to the GI folks[1] and left ours on the table because we were second to file. The original patent application was amended later to add the information required to make human factor VIII. So we got into an interference--that's one of the things I work on all the time--where we said, "Look, we got the gene for human factor VIII before these guys. They did not have an enabling way of making it before their amended application was filed. We were the first ones to file a patent application with the full-length human factor VIII.. The patent application that they first filed is no good because it doesn't have the sequence of human factor VIII." Some decisions had came out that when you're

[1]JJ Toole and E Fritsch, "Human factor VIII:C gene and recombinant methods for production," U.S. Patent 4,757,006, issued July 12, 1988.

talking about patenting DNA molecules, you have to have the sequence of the DNA molecule before you can file a patent, and these guys didn't have that. They had a piece of porcine DNA and claimed that they could use that to get the sequence of human factor VIII. So we had this interference litigation before the United States Patent Office, and we won.

Hughes: On that point?

Kleid: On that point. We went from the junior party applicants against the senior party patentee and knocked out the senior party's patent, and we were awarded the patent, and their patent rights were taken away.

In the meantime, Bayer went nuts, so to speak. They said, "Oh, my God, we're going to be locked out of the market because GI has a patent and we don't." So Bayer agree to a deal with GI and its partner Baxter that said that GI would give Cutter/Bayer a royalty-free license in trade for a royalty-free license under Genentech's patent rights. In other words, it was a royalty-free cross license, which means that neither party pays the other anything, and they are both in the market. So Genentech gets royalties from Bayer, and it gets absolutely nothing from Baxter, thank you very much.

Recently, Cutter/Bayer have had problems making factor VIII. The FDA shut them down. Now they're just a very small part of the market.

Hughes: What was the problem?

Kleid: It apparently arose because the FDA claimed they were not following good manufacturing practices. A company is required to report to the FDA exactly how the product is made, every single detail. Sometimes the FDA visits the company's facilities and checks this out, and reviews records. If they find that there has been some little change here or there, even though it might not make any difference, they might claim, "You're not following the protocol you agreed to." So Bayer is not selling very much factor VIII these days.

A New Type of Factor VIII

Kleid: In the meantime, GI has developed a new way of making factor VIII. There's a part right in the middle of the factor VIII molecule, called the B-domain, that is not required for activity. About half of the molecule, right in the middle, you can cut out and throw away. Back in 1984-1985 GI and Genentech developed a process to make a version of factor VIII without the B- domain. It's called the B-domain deleted factor VIII. That version of factor VIII gets made in nice high quantities.

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Kleid: Cutter/Bayer didn't want to work on this B-domain deleted factor VIII product even though we had given them an exclusive license to make and sell it. They never developed it. In the meantime, GI developed a product called Refracto(TM), which got approved a couple of years

ago, and in 2001 they first started selling it. Apparently, they are gradually going to become the market leader.

We have another interference with them in order to determine who had the idea of a B-domain deleted factor VIII first. That's another one of the interference projects I'm working on right now. GI got a patent issued on the B-domain deletion,[1] and again we were the junior party applicants. We were junior because we had a patent application on file for the full-length factor VIII, but we didn't put in the idea of getting rid of the B domain. We did that project a bit latter in 1984-1985, along with other kinds of factor VIII variants. So in the interference we have taken evidence from all the scientists from both sides who were involved with the GI and Genentech projects and put in all the evidence as to who thought of it and who did it first. That will be looked at by a patent office judge this summer.

Monoclonal Antibodies

[Interview 6: March 1, 2002] ##

Early Companies

Hughes: I want to start back about the time that Genentech was formed when there were two interests in the new genetic technologies in terms of commercial potential. One of course was recombinant DNA. The other one was monoclonal antibodies, and some companies were formed in the late 1970s based on monoclonals. Was a monoclonal-based stream of products ever contemplated in those early days at Genentech?

Kleid: First, who was doing it when we first started? There was a company called Hybritech, and its main emphasis was on developing diagnostic tests using antibodies, monoclonal antibodies in particular. There was another company called Monoclonal Antibodies here in the Bay Area that was in the same area. Hybritech had a patent battle with Monoclonal Antibodies on using monoclonals to do sandwich assays. At first, they lost that battle, and the company's stock went to the ground, and Eli Lilly bought them. Then the case got reversed, and Monoclonal Antibodies ended up going out of business. Lilly has done very well with Hybritech. It's still in southern California but it's called Eli Lilly. It develops assays for all kinds of diagnostic indications.

Another interest was making therapeutics out of monoclonal antibodies, in particular immunotoxins; those became known as "magic bullets." There was quite a group at Stanford interested in them, and they formed a company, and then that company was sheltered by Cetus. It was called Cetus Oncogene or something.

Hughes: Cetus Immune.

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[1]JJ Toole "Novel procoagulant protein" U.S. Patent 4,868,112 issued September 19, 1989.

Kleid: Cetus Immune. Probably formed in '82, but '83 was when they really got going.

Genentech's Initial Policy: Monoclonals As Tools Not Products

Kleid: Genentech, of course, saw what was going on in the monoclonal antibody area but thought that trying to prepare antibodies using hybridomas wasn't something that we were going to get deeply into. But they were important research tools. So very early on we were making monoclonal antibodies against our products, using those to isolate proteins, and developing antibodies and assays using them because we knew that they would be part of making a therapeutic; the antibody would be either part of the quality control or part of the purification or part of the assay. So it was part of the business. But monoclonal antibodies weren't something that we were going to make and sell as projects, nor were we going to get into diagnostics.

Hughes: Why not?

Kleid: Well, I think mostly because we were more interested in the therapeutic products that we were working on, in particular the interferons, tPA, tumor necrosis factor, gamma interferon. Those things had huge numbers associated with them. If those drugs worked for curing cancer or curing what they were designed for, they would dwarf anything with monoclonal antibodies. So that's probably one of the main reasons we didn't really focus on that very much.

Then, in '82 or '83, Art Riggs from the City of Hope came up to Genentech and said that he would like to pick out a monoclonal antibody and clone the gene for it and see if we could prepare monoclonal antibodies using recombinant technology. The reason he wanted to do that was the possibility of adding different sequences onto the antibodies, or one of the other ideas was mixing and matching antibody sequences from different species, in particular changing a murine antibody into a human antibody using genetic engineering.

Cloning Antibody Genes at Genentech

Kleid: One of the interesting areas then was you could inject into a mouse an antigen and the mouse would make an antibody to it. But if you tried to use that antibody in people, you would make antibodies to the mouse antibodies so it wouldn't be useful as a drug. Riggs's idea was maybe you could clone the human antibody and the mouse antibody and somehow mix and match so that they would still bind to the antigen, but they wouldn't get recognized as foreign by the body. He wanted to know if Genentech would be interested in working on something like that.

We were very lukewarm because we were busy with a lot of other things. But Herb Heyneker <u>was</u> interested in antibodies enough to help out. Art came up to Genentech and worked on trying to isolate messenger RNA from hybridoma cell lines. After that trip he either contacted or was contacted by a young scientist in Israel, Shmuel Cabilly. He wanted to come to America and work with Art. They exchanged some letters back and forth and settled on a

project involving genetically engineered antibody genes. So Cabilly came to Art's lab at the City of Hope. With Genentech's financial help to pay for this guy's salary and equipment, they started working on cloning the genes for antibodies.

The first question they had was what antibody should they clone. They decided to work on one that was developed by another scientist at City of Hope, Dr. John Shively. He studied an important protein involved with cancer cells, the antigen called CEA, carcinoembryonic antigen, which was expressed on cancer cell surface. It is a very complex molecule that had been studied for at least five or six years, a lot of that work at the City of Hope. He and his group had made a number of monoclonal antibodies that bound to CEA. They thought, if we're going to go to the trouble of cloning an antibody, let's clone one that's relevant. So he said, "Why don't you guys do this one." He and his group worked with Art and Shmuel and gave them the hybridoma that made anti-CEA. They prepared messenger RNA, and they tried to clone cDNA that they had made from the message for that antibody. But Cabilly couldn't do it. Every time he cloned cDNA from his messenger RNA sample, it would be some kind of junk antibody. It turns out that although you can make a hybridoma cell line that expresses only one antibody, they make lots of messenger RNA that sort of don't work. It's very complicated. It turns out to be pretty easy to clone cDNAs encoding antibody sequences that are not of interest.[1]

After about a year or so of working on this, Cabilly came up to Genentech with his project and worked in Herb Heyneker's lab with another one of his co-workers, Bill Holmes. They took another look at the project and decided to synthesize little pieces of DNA to help them clone this. Bill Holmes eventually cloned the messenger RNA for this antibody.[2] The next step, once you got the gene, was to see if you could make antibodies. The antibody is made up of four chains: two copies of the light chain and two copies of the heavy chain, and they associate into a "Y" shape. The out-stretched arms of the "Y" are the business ends. The straight part interacts with the other parts of the cell and is more species specific. The back end of the mouse antibody would be interact with mouse things, and the back end of the human antibody would interact with human things.

The first step was to clone the cDNAs encoding the light and heavy chains of this CEA monoclonal, which they did. Then the plan was to hook these cDNAs up so that each would express separate light and heavy chains. They put these two cDNA chains into vectors and put the vectors into *E. coli* and actually made some light chain in one *E. coli* and heavy chain in another *E. coli*. But the chains were insoluble, and they would lead to globules, just like the insulin that we talked about. They worked with Ron Wetzel, who helped in the Lilly insulin project, and he was able to dissolve these chains and renature them into the antibody. Then Cabilly got the idea, why don't I express both the light and heavy chains in the same cell? Then we'll have just one step of growing the cell up, dissolving the chains, and then getting the

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[1]S Cabilly, AD Riggs, "Immunoglobulin transcripts and molecular history of a hybridoma that produces antibody to carcinoembryonic antigen," *Gene* 40, 157-61 (1985).

[2]S Cabilly, AD Riggs, H Pande, JE Shively, WE Holmes, M Rey, LJ Perry, R Wetzel, HL Heyneker, "Generation of antibody activity from immunoglobulin polypeptide chains produced in *Escherichia coli,*" *Proc Natl Acad Sci U S A* 81, 3273-7 (1984).

antibody to reform by using refolding steps. That worked a bit, and they were able to recreate antibody-binding activity that way.[1]

The Cabilly Antibody Patent and the Celltech Interference

Kleid: On April 8 of '83, Genentech filed a patent application on the process of expressing the light and heavy chains in the same cell and demonstrating activity. At the same time, a group at Celltech in England started on that project, and they filed a patent application two weeks before us.[2] The two applications led to two patents that issued on the same day.[3]

Hughes: On CEA or on the cloning?

Kleid: On the cloning and expression part. They had gotten plasmid with DNA encoding their antibody from somebody who had already cloned the cDNA for it. They hooked up that cDNA for expression, and they were able to make a little bit of the light chain. They filed their patent application with that experiment in it. Over the next year, they did the heavy chain and hooked it up for expression in yeast cells. They re-filed their patent application (a so-called C-I-P), with lots more information in it, including the yeast work. Our first application (April 1983) had all the work we had done up to that point. We were able to make antibodies from the chains made in *E. coli*. In 1989 their patent and our patent issued on exactly the same day. I don't know what the patent office was thinking. Our patent claims were more limited because we had claims to the details of what we actually did. We also had claims to the idea of making chimeric antibodies, whereas the patent claims from Celltech were directed to the expression of the light and heavy chains in the same cell. So their patent claim were simple: the invention was the expression of the light and heavy chains in the same cell.

Genentech looked at that and said, "Wait a second, we did that before you guys." So we got into a patent interference. (That's how I know about the whole project). We filed a "Cabilly" patent application and wrote claims like theirs because our application described that broad invention also. In 1991, the patent office then put our application into an interference contest with the Celltech-issued patent. The question to be answered was, who invented this first, Cabilly et al. or Boss et al. We submitted our information showing that we had started working on this long before the other side did. The patent office interference judge looked at the evidence we submitted and said, "Well, I don't like your proofs. Your evidence consists of

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[1]The U.S. application led to: S Cabilly, HL Heyneker, WE Holmes, AD Riggs, RB Wetzel "Recombinant Immunoglobulin Preparations," U.S. Patent 4,816,567, issued March 28, 1989.

[2]MA Boss, JH Kenten, JS Emtage, CR Wood, "Polypeptides or proteins and processes for their production," British application GB 8398235, filed March 25, 1983.

[3]A C-I-P of the British application GB 839823, e.g. PCT/GB84/00094, led to: MA Boss, JH Kenten, JS Emtage, CR Wood, "Polypeptides or proteins and processes for their production," U.S. Patent 4,816,397, issued March 28, 1989.

xeroxed copies of notebook pages that I can't even read."[1] Dr. Cabilly had scribbled on the page, so it was difficult to figure out anything, and the copies were really bad. The judge said, "I can't read these things; I'm throwing them in the trash. Now you don't have any proof that you did it first, so you lose." That judge took until 1997 to decide that. The interference began in 1991, and then the PTO judge came up with this decision years later.

We appealed the decision in District Court in a 146 Action, a type of litigation where you can complain about a decision made at the patent office. You can also put in more information. So in 1999-2000 we started down the road of doing that. We brought in our story with nice copies of the relevant notebooks and other documents. We interviewed all the witnesses--Art Riggs, Cabilly, and all the people that worked on this project, and they were deposed by the attorneys that represented Celltech. The issue was, could Genentech prove that we had the invention two weeks before we filed our own patent application, a day before Celltech's application was filed in England? It wasn't really an issue as to what Boss et al. had done or not done; they didn't have to prove anything.

Dr. Cabilly came back to the U.S. from Israel to give his deposition. Just before one of these depositions, I was talking to him about his notebooks and other documents that he provided us. I also asked him a bit about the process of how the patent application got drafted and filed back in 1983. He said, "I have a draft of the patent application in my garage in Israel." I nearly fell on the floor. Most everybody throws the draft patent applications away. We didn't have any idea that he had a draft patent application from that time period. He returned to Israel and sent the draft back to his City of Hope attorney who made copies for Genentech and Celltech, and we put that into evidence. Everything about the invention was all written there, so that was all the evidence we needed to show that we had the idea before Celltech submitted its British application. During this 146 Action litigation, Celltech decided to settle the case because they were obviously not going to prevail. So now we have that patent with the broad claims. It issued a few months ago.[2]

Chimeric and Humanized Antibodies

Kleid: In the intervening time from '86 to 2002, there's been a huge amount of work on making antibodies using genetic engineering. One of the first experiments published in this area was in 1984 from Stanford.[3] This project involved cloned human and mouse antibody genes and

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[1]Cabilly v Boss Interference No. 102,572; 55 USPQ2d 1238 (BPAI 1998).

[2]S Cabilly; HL Heyneker; WE Holmes; AD Riggs; RB Wetzel, "Methods of producing immunoglobulins, vectors and transformed host cells for use therein," U.S. Patent 6,331,415, issued December 18, 2001.

[3]SL Morrison, MJ Johnson, LA Herzenberg, VT Oi, "Chimeric human antibody molecules: Mouse antigen-binding domains with human constant region domains," *Proc. Natl. Acad. Sci USA* 81, 6851-55 (1984).

mixing and matching: take the DNA encoding the human part, the bottom part of the "Y," and hook it up to the DNA encoding the mouse business end. Use that DNA construct to make chimeric antibodies. That was found to be a very useful idea. In fact, one of our most important products, Rituxan(TM), is a product like that.[1] It reacts with a receptor called CD20.[2] CD20 is a membrane-bound receptor for iron which the cell needs to pump iron in. The company that developed this product, IDEC Pharmaceuticals, was started by ex-Genentecher, Bill Rastetter. They developed a monoclonal antibody that bound to the CD20 receptor. That receptor is found in high amounts on B-cells that make antibodies. One important cancers is B-cell lymphoma. These B-cells just start growing like crazy. If you can interfere with that, then you can do something about that cancer. There were some early studies in humans concerning an antibody that reacted with that receptor. It was active against the cancer in high doses, but it would develop antibodies against the antibodies, because it was a mouse antibody.[3] So they converting it to a chimera where part is human and part is mouse, and then there isn't a big problem with the antibodies. That has been a huge success.[4]

Hughes: Was it Genentech that worked out the technology to produce humanized antibodies?

Kleid: Well, the chimeric antibody idea was invented by Genentech and first commercialized by Genentech and IDEC Pharmaceuticals.[5] There still may be some recognition by the human immune system to that the mouse part; its not quite right. The next step is a humanized antibody. Here the binding specificity of the monoclonal antibody can be developed in any species, although most are murine monoclonal antibodies. The sequence of the binding region is then determined, usually by sequencing the DNA encoding the antibody. There are three little sites called complementarity-determining regions (or CDRs) on each of the outstretched arms of the antibody. The light and heavy chains come together to form these CDRs. These three little CDR sequences, which are eight or twelve amino acids long, are separated by sequences from the human antibody called "framework regions." What is done is to model these sequences on a computer that can turn the sequence data into three-dimensional representations based on the crystal structure of antibodies. From this you can figure out pretty

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[1]DR Anderson, N Hanna, JE Leonard, RA Newman, ME Mitchell, WH Rastetter, "Therapeutic application of chimeric and radiolabeled antibodies to human B lymphocyte restricted differentiation antigen for treatment of B cell lymphoma," U.S. Patent 5,736,137.

[2]DG Maloney, TM Liles, DK Czerwinski, C Waldichuk, J Rosenberg, A Grillo-Lopez, R Levy, "Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma," *Blood* 84, 2457-66 (1994).

[3]OW Press, F Appelbaum, JA Ledbetter, PJ Martin, J Zarling, P Kidd, ED Thomas, "Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas," *Blood* 69, 584-91 (1987).

[4]AJ Grillo-Lopez, CA White, BK Dallaire, CL Varns, CD Shen, A Wei, JE Leonard, A McClure, R Weaver, S Cairelli, J Rosenberg, "Rituximab: the first monoclonal antibody approved for the treatment of lymphoma," *Curr Pharm Biotechnol* 1, 1-9 (2000).

[5]S Cabilly et al., U. S. Patent 4,816,567; Rituxan(TM): DR Anderson et al., U.S. Patent 5,736,137.

closely what the CDR sequences are and what they might look like in three dimensions. Using this information, a sequence is designed for the antibody created. It would be best to have as little mouse sequences as possible--to reduce any immune response. Once the structure is chosen, it's up to the molecular biologist to make a gene encoding that antibody and create a cell line that expresses that sequence. That is a humanized antibody--it's the next level of sophistication, and this was used by Genentech scientists for Herceptin(TM).[1] For this product, all you need is the data from a mouse antibody that you really really like. You can take that data and design your own antibody on the computer, just design the DNA sequence. You can design exactly what you want and maybe make six or ten of these different antibodies and test them to see if the combining regions still work.

Hughes: How innovative a role did Genentech play in this area?

Kleid: Well, I think we contributed a lot all the way along. We get some credit for the first step, cloning antibodies and having the idea for chimeric.[2] Then for making the chimeric, I think the first was the group at Stanford with Len Herzenberg. He had a couple of younger researchers with him, Sherie Morrison and Vernon Oi who made the first recombinant chimeric antibody.[3] Then I would say the researchers in England, led by Greg Winter (he worked with the original Georges Kohler and Cesar Milstein group that first used hybridomas), developed this next level of sophistication called CDR grafting.[4] Some people credit the group at Protein Design Labs for computer modeling.[5]

Throughout that period Genentech was working on these things. We had here at Genentech Paul Carter and his team made our humanized antibody Herceptin(TM). Len Presta did the computer modeling.[6]

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[1]P Carter, LG Presta, "Immunoglobulin Variants," U.S. Patent 5,821,337.

[2]S Cabilly, HL Heyneker, WE Holmes, AD Riggs, RB Wetzel, "Recombinant Immunoglobulin Preparations," U. S. Patent 4,816,567.

[3]SL Morrison, VT Oi, "Genetically Engineered Antibody Molecules," *Advances in Immunology* 44, 65-92 (1989).

[4]GP Winter, "Recombinant altered antibodies and methods of making altered antibodies," U.S. Patent 5,225,539; PT Jones, PH Dear, J Foote, MS Neuberger, G Winter, "Replacing the complementarity-determining regions in a human antibody with those from a mouse," *Nature* 321, 522-525 (1986).

[5]CL Queen,WP Schneider, HE Selick, PW Payne, NF Landolfi, JF Duncan, NM Avdalovic, M Levitt, RP Junghans, TA Waldmann, "A Humanized antibody that binds the interleukin 2 receptor," *Proc. Natl. Acad. Sci. USA* 86, 10029-33 (1989).

[6]P Carter, L Presta, CM Gorman, JB Ridgway, D Henner, WL Wong, AM Rowland, C Kotts, MR. Carver, HM Shepard, "Humanization of an anti-p185HER2 antibody for human cancer therapy," *Proc. Natl. Acad. Sci. USA* 89, 4285-9 (1992).

Therapeutic Monoclonal Antibodies, Including Rituxan

Hughes: What was the first therapeutic use of monoclonals?

Kleid: Well, I think the first monoclonal that got approved as a therapy is called OKT3, and it's a regular old murine monoclonal against the T3 antigen on human T cells. This can be used until you get an immune response. It's for acute treatment of transplant rejection.[1] The next major one in clinical trials was Campath-1H, work sponsored by Burroughs-Wellcome, now Glaxo.[2] They developed a humanized antibody that binds CD-52 on T cells and B cells. They brought that to the clinic and tested that in numerous clinical trials during the mid-1990s, and it didn't work that well for cancer in their trials. So Burroughs-Wellcome sold the whole project to a little company, LeukoSite. Then that company was bought by Millennium in Boston. They continued on more limited indications for the same antibody in collaboration with yet another small company, ILEX Oncology.[3] The product was finally approved by the FDA in 2001. Marketing of the antibody for B-cell chronic lymphocytic leukemia began in May 2001 and is marketed by Schering AG and Berlex for ILEX. I don't know how well it works.

The first major monoclonal therapies were Rituxan(TM) and Herceptin(TM), both from Genentech. They are the first genetically engineered monoclonal antibodies, and they're both directed toward antigens on cancer cells. Rituxan is for B-cell lymphoma; Herceptin is for breast cancer.

Hughes: Do you want to say something about their development?

Kleid: I don't know very much of the story of Rituxan because the original work was done at IDEC. They were very interested in having a monoclonal against CD20, and they noticed that it really had a big impact on growth of these B-cell lymphoma cells.[4] They came to Genentech and convinced us to work with them. As I mentioned, the founder and president of that company was an ex-Genentecher, Bill Rastetter. While at Genentech he was trying to do genetic engineering for agricultural projects. He stayed close with Bob Swanson and our management. We decided to finance that project very early on when the company was really small and make an investment in the company. If it worked out, we would share the profits with them, and

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[1]AB Cosimo, RC Burton, R Cloven et al., "Treatment of acute renal allograft rejection with OKT3 monoclonal antibody," *Transplantation* 32, 535 (1981).

[2]G Hale, MJ Dyer, MR Clark, JM Phillips, R Marcus, L Riechmann, G Winter, H Waldman, "Remission induction in non-Hodgkin lymphoma with reshaped human monoclonal antibody CAMPATH-1H," *Lancet* 2, 1394-9 (1988); H Waldmann, "A personal history of the CAMPATH-1H antibody," *Med. Oncol* 19 supp:S3-9, (2002).

[3]FJ Dumont, "Alemtuzmab (Mellennium/ILEX)," *Curr Opin Investig Drugs* 1, 139-60 (2001).

[4]OW Press, F Appelbaum, JA Ledbetter, PJ Martin, J Zarling, P Kidd, ED Thomas, "Monoclonal antibody 1F5 (anti-CD20) serotherapy of human B cell lymphomas," *Blood* 69, 584-91 (1987).

maybe our investment in IDEC stock would go up in value. In 2002 Genentech and IDEC will sell about a billion dollars worth of this anti-cancer drug.

We helped to do the clinical studies for Rituxan and to scale it up for manufacturing. We make the antibody in the factory in Vacaville in Chinese hamster ovary cells. Chinese hamster ovary cells make this humanized antibody, actually a genetically engineered molecule that doesn't exist in nature. It's really fantastic when you think about it. First, develop a monoclonal against the CD20; next, get the gene from the mouse that makes it; then, design the genes needed and put those genes into vectors; after that, put the vectors into Chinese hamster ovary cells; then, grow those cells in 10,000-liter fermenters, and finally, recover this antibody from the media. Pretty amazing! It's the same story for Herceptin.

Research on Growth Factors

Axel Ullrich's Contributions

Kleid: The story of Herceptin goes back to the early days of Art Levinson and Axel Ullrich here at Genentech. One of Axel Ullrich's projects was to clone the gene for the epidermal growth factor, EGF, and also NGF, nerve growth factor. Those were his very first projects after insulin, because they're kind of related. IGF, insulin-like growth factor, is another one. They're all small peptides that bind to cells of a particular type and make them grow. You can imagine, epidermal growth factor is responsible for making epidermal cells grow; NGF makes nerves grow; and insulin-like growth factor makes cartilage cells grow. He cloned the genes for those, or made them using synthetic DNA.[1]

Axel was very interested in how they bind to the cell and turn the cell on. He was the first one to clone the insulin receptor. Then he cloned the EGF receptor. He was working with a scientist in England named Michael Waterfield, and they had a monoclonal antibody against that epidermal growth factor receptor. So they were able to purify enough of this receptor to make amino acid sequence data. They looked at the amino acid sequence data, and they were very surprised to find that it was related to an oncogene.. The oncogene was named v-erb-B.[2] It's the avian erythroblastosis virus oncogene. It was known in *in vitro* studies that you could take the virus, infect cells, and they would become cancer cells; they would just grow like

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[1]A Gray, TJ Dull, A Ullrich, "Nucleotide sequence of epidermal growth factor cDNA predicts an 128,000-molecular weight protein precursor," *Nature* 303, 722-25 (1983); A Ullrich, A Gray, C Berman, TJ Dull, "Human beta nerve growth factor gene sequence highly homologous to that of mouse," *Nature* 303, 821-25 (1983); A Ullrich, C Berman, TJ Dull, A Gray, JM Lee, "Isolation of human insulin-like growth factor I gene using a single synthetic DNA probe," *EMBO Journal* 3, 361-363 (1984).

[2]J Downward, Y Yarden, E Mayes, G Scrace, N Totty, P Stockwell, A Ullrich, J Schlessinger, MD Waterfield, "Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences," *Nature* 307, 521-27 (1984).

crazy. That was kind of the simple definition of an oncogene--a gene sequence that would cause a cell to transform into a cancer cell.

Epidermal growth factor receptor has amino-acid sequences that look like this oncogene. The relationship between how oncogenes work and how growth factor receptors work is explored in several publications from Waterfield and Ullrich.[1] Axel's group went on to clone the gene of the epidermal growth factor receptor and to determine its structure,[2] then of the insulin receptor.[3] They each have the same characteristics: a part that goes outside the cell, a transmembrane region, and another part inside the cell. The inside domain has tyrosine kinase activity. The receptor binds to something on the outside[4] and sends a signal to the inside, and that signal causes phosphorylation of the receptor inside the cell. That phosphorylation signal somehow leads to another signal in the nucleus of the cell that activates certain genes, and this causes the cells to grow.

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Kleid: Ullrich's discovery with Waterfield was a major finding. There were a number of these genes, for example, *ras, sarc, neu,* and *fos*; there were maybe ten of these oncogenes associated with tumor viruses. Now there was a connection between the oncogene and growth factor receptor. So that was a really big deal, and we were really excited about it. Ullrich wrote a lot of papers on that and got to be a very famous young scientist for establishing that connection..[5]

Hughes: That's very basic science. What was Bob Swanson's reaction?

Kleid: "Axel's off doing basic research. What does that have to do with anything?" [chuckles]

Hughes: Did he get in hot water with Swanson, or did the prestige of his science pull him out of the fire?

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[1]TA Libermann, HR Nusbaum, N Razon, R Kris, I Lax, H Soreq, N Whittle, MD Waterfield, A Ullrich, J Schessinger, "Amplification, enhanced expression and possible rearrangement of the EGF receptor gene in primary human brain tumours of glial origin," *Nature* 313, 144-147 (1985).

[2]A Ullrich, L Coussens, JS Hayflick, TJ Dull, A Gray, AW Tam, J Lee, Y Yarden, TA Libermann, J Schlessinger, J Downward, ELV Mayes, N Whittle, MD Waterfield, PH Seeburg, "Human epidermal growth factor receptor cDNA sequences and aberrant expression of the amplified gene in A431 epidermoid carcinoma cells," *Nature* 309, 418-425 (1984).

[3]A Ullrich, JR Bell, EY Chen, R Herrera, LM Petruzzelli, TJ Dull, A Gray, L Coussens, Y.-C Liao, M Tsubokawa, A Mason, PH Seeburg, C Grunfeld, OM Rosen, J Ramachandran, "Human insulin receptor and its relationship to the tyrosine kinase family of oncogenes," *Nature* 313, 756-761 (1985).

[4]Insulin or EGF in these cases.

[5]A Ullrich, "Growth factor receptor function and role in oncogenesis," *Experimental Medicine* 6, 32-35 (1988).

Kleid: Well, he did do the projects that Swanson wanted--EGF and NGF. Many years later nerve growth factor became a project at Genentech for treatment of nerve damage,[1] although the project eventually died at Genentech because a phase III clinical trial didn't work out that well.

Herceptin

Kleid: Axel's interest was in this basic research area, which leads us to Herceptin. As I said, his group did the cloning of the epidermal growth factor receptor. The human version is called HER--human epidermal growth factor receptor. When they were cloning that gene, they found there was another gene that was related but not the same. They call that HER2.[2] At about that time, some of his collaborators, some at MIT, were studying oncogenes. In the rat they found an oncogene that they named *neu* which came from a neuroblastoma, or some kind of an oncogene that made brain cancer in rats.[3]

It turned out that HER2 and neu were very close in sequence; one was from a rat, one was from a human. Then a group in Japan, using the erythroblastosis gene, cloned a gene out of humans that was very closely related to that, and they called that c-erbB-2, for cellular version of the viral oncogene v-erbB2.[4] Genentech called it HER2 for "Human" epidermal growth factor receptor number 2. Epidermal growth factor receptor, of course, binds to epidermal growth factor. But the ligand to epidermal growth factor receptor 2 was not known. Was there some other undiscovered human growth factor? They didn't know. And in fact now we know that nothing binds to HER2. It has the extracellular part, but it doesn't seem to get turned on by a growth factor. Instead, it gets turned on when it's present in the same cell with HER1, or when its present in elevated amounts. If one HER2 molecule and another HER2 snuggle up to each other, they can turn on each other's tyrosine kinases. This can also be done with HER1.

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[1]SC Apfel, JA Kessler, BT Adornato, WJ Litchy, C Sanders, CA Rask, "Recombinant human growth factor in the treatment of diabetic polyneurophathy; NGF Study Group," *Neurology* 51, 695-702 (1998).

[2]L Coussens, TL Yang-Feng, Y.-C Liao, E Chen, A Gray, J McGrath, PJ Seeburg, TA Libermann, J Schlessinger, U Francke, A Levinson, A Ullrich, "Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene," *Science* 230, 1132-1139 (1985).

[3]AL Schechter, DF Stern, L Vaidyanathan, SJ Decker, JA Drebin, MI Greene, RA Weinberg, "The neu oncogene: an erb-B-related gene encoding a 185,000-Mr tumour antigen," *Nature* 312, 513-6 (1984).

[4]K Semba, N Kamata, K Toyoshima, T Yamamoto, "A v-erbB-related protooncogene, c-erbB-2, is distinct from the c-erbB-1/epidermal growth factor-receptor gene and is amplified in a human salivary gland adenocarcinoma," *Proc. Natl. Acad. Sci. USA* 82, 6497-501 (1985).

In the last few years HER3 or HER4 have been found, which are also closely related, and they can also participate.[1]

When we were trying to figure out what HER2 was, Axel had a collaboration with Dennis Slamon, an MD at UCLA. He found that breast-cancer cells from some of the worst beast cancers had a lot of copies of the HER2 gene. He studied breast cancers from women and looked to see how much of this HER2 DNA they had. It turned out that there was a correlation between how bad their breast cancer was and how many copies of this gene they had.[2] They found that one-third of breast cancer has extra copies of the HER2 gene. What's causing those cells to grow like crazy is that they have extra HER2 genes in the nucleus. The thought was, maybe there's a way to treat breast cancer if we can target those cells for destruction.

Axel's group took their gene encoding HER2 and put it into another cell and expressed it and used that to develop monoclonal antibodies against that receptor. Then they found a whole panel of these monoclonal antibodies, and they tested them to see which ones were the best. They found a few that not only bound to HER2 but also slowed the cells down. The monoclonal binding somehow impacted the ability of those cells to replicate. They wrote a paper on all that.[3] Then all the researchers got <u>really</u> excited because now you had a correlation between the presence of HER2 and cancer, and you had a monoclonal antibody that did something. So Axel was really excited about this project. But Genentech, in its wisdom, was not very excited.

Hughes: Why?

Kleid: Because they were too excited about other projects that were supposed to go to the moon, like tPA, tumor necrosis factor, and gamma interferon.[4]

Hughes: Axel alone was working on Herceptin?

Kleid: He was. So he got fed up and decided to quit Genentech and start his own company (Sugen), which he did. He went back to Germany.

Hughes: To develop Herceptin?

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[1]Y Yarden, MX Sliwkowski, "Untangling the erbB signalling network," *Nature Reviews, Molecular Cell Biology* 2, 127-137 (2001).

[2]DJ Slamon, GM Clark, SG Wong, WJ Levin, A Ullrich, WL McGuire, "Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene," *Science* 235, 177-82 (1987).

[3]RM Hudziak, GD Lewis, M Winget, BM Fendly, HM Shepard, A Ullrich, "p185HER2 monoclonal antibody has antiproliferative effects in vitro and sensitizes human breast tumor cells to tumor necrosis factor," *Mol. Cell Biol.* 9, 1163-72 (1989).

[4]Genentech's pioneering work on tyrosine kinase receptors and oncogenes, such as HER2, gets no mention in a Genentech's annual reports until 1989, the year after Dr. Ullrich left the company for the Max Plank Institute in Munich, Germany.

Kleid: That was the project that he wanted to do most of all. Before he left, we wrote a patent on the monoclonal antibody that he had developed.[1] After he left, Dr. Slamon at UCLA and Axel, now in Germany, started publishing all over the place about the correlation of HER2 with breast cancer,[2] and all of a sudden Genentech said, "Wait a second, this is a really good project." There was a brouhaha between Axel and Genentech, and Genentech said, "You developed that here. It's staying here, and we are going to work on it." Axel continued to work with tyrosine kinases at Sugen, but not on a project involving antibodies against HER2. Genentech decided to go ahead and develop ours.[3] Clinical studies done in 1991 with the murine antibody against HER2, (known as 4D5), were encouraging, so it was decided to "humanize" this antibody.[4] They cloned the gene encoding 4D5, and they looked at the sequences that were part of the business end, and they modeled it on a computer. They designed a set of humanized monoclonals and tested them all, and one of them turned out to be the best. In fact, they have data that show that it binds even tighter than the mouse monoclonal. They put that gene into Chinese hamster ovary cells and developed what we now call Herceptin(TM). It just worked like gang busters from the very first try. People with breast cancer heard about it, and everybody wanted to be in the phase III clinical trials. We had demonstrations demanding that we make more. I think we ended up having some sort of lottery when we first started our clinical trials.[5]

We decided to join forces with the people that were pressuring us to make Herceptin available. There ended up being a tremendous synergy between Genentech and the cancer activist community. They powered Herceptin through the clinical trials and to the FDA, and they celebrated with us when it got approved. It's just a tremendous story. That occurred about

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[1]RM Hudziak, HM Shepard, A Ullrich, "Method of treating tumor cells by inhibiting growth factor receptor function,"USSN 143,912, filed Jan 12, 1988 (WO 89/06692), now RM Hudziak, HM Shepard, A Ullrich, BM Fendly, "Monoclonal antibodies directed to the HER2 receptor,"U.S. Patent 5,677,171.

[2]DJ Slamon, W Godolphin, LA Jones, JA Holt, SG Wong, DE Keith, WJ Levin, SG Stuart, J Udove, A Ullrich, et al., "Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer," *Science* 244, 707-12 (1989); PG Natali, MR Nicotra, A Bigotti, I Venturo, DJ Slamon, BM Fendly, A Ullrich, "Expression of the p185 encoded by HER2 oncogene in normal and transformed human tissues," *Int J. Cancer* 45, 457-61 (1990).

[3]HM Shepard, GD Lewis, JC Sarup, BM Fendly, D Maneval, J Mordenti, I Figari, CE Knotts, MA Palladino, A Ullrich et al., "Monoclonal antibody therapy of human cancer: taking the HER2 protooncogene to the clinic,"*J Clin Immunol* 11, 117-27 (1991).

[4]P Carter, L Presta, CM Gorman, JB Ridgway, D Henner, WL Wong, AM Rowland, C Kotts, MR Carver, HM Shepard, "Humanization of an anti-p185HER2 antibody for human cancer therapy," *Proc. Natl. Acad. Sci.USA* 89, 4285-9 (1992).

[5]Nine hundred women were treated with Herceptin in clinical trials by 1996.

two or three years ago.[1] Herceptin is a $300- or $400-million-a-year drug. So that's our oncogene-to-antibody story.

Hughes: So Herceptin has turned out to be quite a money maker for Genentech.

Kleid: Herceptin and Rituxan account for more than half of our sales.[2]

Genentech As an Industry Pioneer

Hughes: Would you comment on Genentech's pioneering role in many aspects of biotechnology?

Kleid: I could try. I think number one has to be that we were the first to apply genetic engineering tools to human health. The vectors of Boyer and Cohen and synthetic DNA were let loose on the pharmaceuticals industry. The fact that we were the first to try this and have survived all this time and have remained the undisputed leader in this technology is a fantastic accomplishment.[3] But what I've noticed from working in the legal area is that the innovator or leader gets a knife in the back from the copycat, the guy behind you. It takes a lot more money and expertise and time to do something first. Others can ride on our coattails and either copy what we have done or make claims that it was they, not Genentech, that made the breakthrough. This has taken a lot away from our bottom line.

Maybe we asked for it. Genentechers wrote everything up in their publications. As footnotes above show, all the breakthroughs are there for everyone to read. So the second one along really has no trouble copying all that. And they do. The type of technology that we use, the DNA itself, gives the copycat a real advantage. Genentechers publish the code for the breakthrough medicine, the whole thing, and then the copycat knows that there are some amino acids that are important to the activity, and there's a whole bunch of others that don't do anything. So they change a few. Most of the copycat products have been just that; they change a few amino acids here and there.[4]

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[1]It was approved for marketing Sept. 25, 1998.

[2]Sales first six months 2002: Herceptin: $181.9 million; Rituxan: $522.5 million; all products: $1 billion.

[3]P Gwynne, "Top Employer, Companies of Choice," *Science* 297, "Careers" supplement (2002).

[4]"Duteplase" is an example of this. A single amino acid substitution, the result of a cloning error, is the only difference between Genentech's tPA and the Wellcome product. *Genentech Inc. et al. v. Wellcome et al.* (CA 88-407, 89-330 D. Del) 14 USPQ2d 1363 (D. Del. 1990), 24 USPQ2d 1782 (D. Del 1992); AD Malcolm, M Keltai, MJ Walsh, "ESPRIT: a European study of the prevention of reocclusion after initial thrombolysis with duteplase in acute myocardial infarction," *Eur Heart J* 17, 1522-31 (1996); ZG Turi, S Goldberg, JK LittleJohn, AC Vander, N Shadoff, R Karlsberg, J Williams, S Butman, ML Stadius, K Wise et al., "Dose-related efficacy and bleeding complications of double-chain tissue

Then the other part is the dynamic between the little companies and the big companies. The big companies have a lot more power, and they can put a lot more people on a project and can change directions more readily than the little guy can.

Hughes: You mean the pharmaceutical industry?

Kleid: Yes, which we consider ourselves part of, but we're still not listed in the same way. We have Amgen and Genentech as the leaders of the biotechnology industry and then all the pharmaceutical companies, which keep getting fewer in number. Now they've got names like GlaxoSmithKline. It's the combination of companies called SmithKline, Beckman, Beecham, Glaxo, Burroughs-Wellcome. They keep merging or buying each other. There are exceptions, of course, like Merck and Lilly, but they also buy smaller companies.[1] So it's much harder for the little biotechnology company to make it.

Right now there must be a hundred biotechnology companies. Only a couple of them are actually making any money. All the rest are surviving by selling shares in what's going to happen in the future. They take investments and they spend the money. If their projects don't work, the stock is worthless. It's a real crapshoot. When we started Genentech, we thought there was only going to be one company focusing on genetic engineering--us. That was going to be it. Then Biogen and other companies came along. We thought, well, they're not going to last long. Some of them have, but through the skin of their teeth. Though clearly a survivor, Biogen is not a very profitable company.

Hughes: Was it naive to think that one company could cover the field? Is that viewpoint a reflection of even Genentech not realizing the power of the technology?

Kleid: We first worked with Eli Lilly. They said, "Well, there's only one drug in all of the pharmaceutical industry that is an injectable protein, and that's insulin. There are a couple little other things. You have a very limited number of molecules you can make." They and Genentech made a list of all the proteins that might have some biological action worth pursuing as pharmaceuticals. Of course the interferons were real exciting; the tPAs were real exciting. The pharmaceutical companies hemmed and hawed, "Okay, those are maybe the exceptions." The plan on the part of the major pharmaceutical companies was to kind of cherry pick the good projects but not to invest too much themselves in the technology.

Now you can see that the exception is the rule. Using genetic engineering we are able to design molecules that don't exist in nature. Lilly designed a useful analog of human insulin called Humalog(TM). Our antibodies are another good example--Herceptin(TM) and Rituxan(TM). In the 1970s and 1980s generally the major pharmaceutical companies never thought of those things. Here we are creating molecules completely from scratch, and it's just

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plasminogen activator in acute myocardial infarction. The Wellcome Tissue Plasminogen Activator Study Group," *Am J Cardiol* 71, 1009-14 (1993).

[1]Eli Lilly bought Hybritech, Inc.

having a tremendous impact. These tools are being applied to all different kinds of cancers, and it's really happening.

Hughes: Do you think we are at the brink of some really exciting times in biotechnology?

Kleid: I think so. My professor at Berkeley, Gunther Stent, said when I took his class in 1969: "Molecular biology is all over. It's too bad you missed it." Then you hear people talk about the days when Genentech did insulin. They say, "Well, that was easy. You guys knew what the proteins were, the biology was understood, and anybody could put those genes together." Wait a second, you had to be there; putting those genes together was not that easy. Cloning synthetic DNA was not that easy since the chemistry wasn't that developed. Factor VIII was beyond the skill of the time and so was interferon and tPA; those were incredibly difficult. Scaling the technology up for manufacturing had never been done!

But in today's world, we have the total human genome sequenced; we have thousands and thousands of genes on little chips, and we can use those chips to see what messages are being made in the cells. We have sort of changed biology into chemistry and really figured out what's going on at the molecular level using these new tools. Tremendous things are happening right now. We have started to do some very, very incredible experiments with those gene chips. There is no question that Genentech, as well as others, have some very powerful ideas on how to use these chips in order to understand how the molecules in our body work so we can figure out how to impact different kinds of diseases.

Hughes: To what degree do you think that Genentech has served as a model or in some cases an anti-model for the biotech industry?

Kleid: Well, I think we've served as a model, especially in respect to Swanson's vision in the early days to be a fully integrated company and to bring a business aspect to molecular biology. Nobody in school ever taught me to write a patent application; nobody talked to me about a business plan; nobody even told me how to write a grant application. You were just pushed out into the academic world and told: "Make some discoveries! Learn something about how life works at the molecular level. That's what being a real scientist is all about!" But wait a second, that's only part of it. Sure I want to add to the body of knowledge, but I also want to do something useful.

I turn that around, saying, "You not only teach and publish, but you actually help the general public with this technology." That was a huge thing to me. I think people really recognized Genentech's contribution, as well as Amgen's with their Epogen(TM). Amgen was another copycat company started right after Genentech that just happened to pick up a project that really worked for them. So is Genentech a model? The idea is to be able to do everything from discovering the drug to marketing it. It's pretty amazing, and only a handful of companies have done that. Personally I think that's too much to ask. The biotech companies of today need to have a more modest vision.

Our early model was to try to stay profitable at all times. As we made our discoveries, we sold them off to pay for our current research so we would be a profitable company all the way through. That worked on a small scale in the beginning. As we grew after the mid-1980s, I

don't know if that was such a great idea because we sold off a lot of really valuable products for a song. If we had them today we'd be ten times bigger.

Hughes: But in the very early days you really didn't have much of a choice, did you? Take insulin, for example. What could Genentech have done other than what it did?

Kleid: Exactly. In the early days, you're right. But as we went along in the 1980s, in the effort to stay profitable we were selling off our products in order to show a profit each quarter, which was really painful.

Hughes: Why was it important to Swanson to stay profitable?

Kleid: He felt that the investment community would stick by us better if we were in the black all the time. I don't think that actually turned out to be the case. What the community was looking for was how much we were going to grow. So even though we were black every single year, when tPA didn't work out they trashed our stock anyway. So it was only on the promise of future products. Being in the red wouldn't have hurt that much at all.

One of the big deals was the limited partnerships for growth hormone and for gamma interferon that we talked about. To raise--what was it?--\$50-80 million. When we bought the project out it cost us \$250 million in Genentech shares to get back the \$80 million that we raised in the partnerships and spent on those projects. It wasn't until 1992 that we actually ended up in the black. Even though on the books we were in the black almost each quarter, in reality there were off bottom-line costs that investors don't look at. That's very controversial today with this Enron situation. There are lots of ways to make your books look like you're in the black when you're really spending your future.

Biotechnology Industry Organization

Hughes: In 1981 the Industrial Biotechnology Association was formed, now known as BIO. I read that Genentech did not join immediately. Do you know anything about that?

Kleid: Yes, a slight bit. When it started, the biotechnology association was composed of little biotech companies, and Genentech wanted to be a pharmaceutical company. The small biotech companies had a different agenda than we had--we wanted to become a fully-integrated pharmaceutical company. Most of the small companies wanted to sell themselves off to another bigger or richer company. They just weren't on the same page with us. Plus intellectual property: We had patents to cover what many of the little companies were doing. Those darn copycats weren't planning on paying us any royalties. Later, BIO became more of an organization to talk to Congress and have some visibility in the political arena. That was fine and was important to us. We gradually became a leader of the organization. As you know, there were quite a few issues with biotechnology and the general public, which continue today.

Hughes: Is it generally felt today that BIO does a good job?

Kleid: I don't know. It's not in my periscope. We have our own lobbyists in Washington, and they watch over certain issues, like the research and development credit and the Orphan Drug Act. There have been a few specific things that help out small companies. So we get behind those issues; try to convince congressmen to keep those things on the books.

Hughes: When Genentech began to have lobbyists in Washington, did it then become less important to be a member of BIO?

Kleid: I think our lobbyists and some of our employees in Washington ended up being major players in BIO.

Reflections on the Interview Process ##

Hughes: When you look back over the six interviews that we've done, is there anything that stands out in the way the story came together or that you would have told differently on your own?

Kleid: Well, I don't think I would have told this story on my own. If I decided to write my own book on Genentech, where would I start? Chances are it would end up being a self-serving biography. Whereas this particular process of talking and hopefully also thinking about what happened is pretty interesting. As you say, we don't know what historians will do with this oral history we are working on. Anybody that tries to read my stuff from cover to cover is going to go nuts. But if somebody really wanted to research a particular aspect of a particular project, there's some material here that they probably wouldn't be able to put together otherwise. How do other people feel?

Hughes: Richard Scheller asked me what use the oral histories serve. One use, as you've touched on, is that they supply details that are difficult to get from other sources or at least would be very tedious to piece together. It may be that the real value of what we're doing today won't become apparent until sometime in the future, maybe when most of us are no longer here and the science has moved on. I hope that what we're doing collectively in this project is giving people of the future some idea of how this science was practiced, the nature of its social context at the outset of a new industry, and the personalities and motives of those involved.

Kleid: I was watching the Discovery Channel a couple nights ago about the building of the Hoover Dam, and what a monumental project that was. Now, you just look at the dam, "Okay, fine, its holding back a lot of water." Then you see the story of how they built it, and it's just absolutely incredible. Luckily, the people that built it are still around so they could tell their story. The biotechnology industry, there's no dam there. How do you piece together this particular industry?

Hughes: We have pieces of the dam all over the geography. [laughs]

Corporations As Organisms

Kleid: Yes. We talked about how this company seems like an organism to me; it's kind of alive. It has its own needs and it has its own agenda that are independent of everybody inside. Maybe you're a VP and you're trying to do your job, but actually you're just answering to the next guy up, and the people below are trying to keep you happy. So who is controlling this organism? The president of the company has an impact, but he hasn't come over here to my office and told me what to do. But he does create an attitude: "We're going to cure some diseases that right now there's no treatment for. That's what our job is. I want you guys to do that." "All right. It sounds like a tall order but we'll give it a try."

It makes for a fantastic organism, when you think about it. Here's one that's truly altruistic, going out there and curing diseases that nobody could cure before. But as an organism, it needs to survive, and it needs to survive by the will of investors and by making a profit, because nobody's going to invest in a company if it's going to lose money forever. They'll just quit on it, and then everybody has to go home. The saddest thing about the biotechnology industry is how many companies have closed their doors. How would you like to work your buns off every single day for five years, and then it turns out that your project didn't quite work out fast enough for the investors, and you had to go home? Everything, all of the work, gets boarded up and sold. Your stock certificate and options--all worth nada. You don't run into that in academia. You try to think of a good idea to work on, or you can go teach. It's such a safe life being an academic scientist--and fun. But here, you really go home if it screws up. Maybe you've invested your own money. Scientists should never do that. Never ever spend your own money on your own research project because you are sure to lose it all. [laughter] Spend other people's money and then hope that it works.

Hughes: Well, what else would you like to say?

Kleid: Well, I enjoyed being with you, Sally. It's really a pleasure to do this process, and you're a big part of it. You're thinking ahead about what we're going to talk about, and it really makes it an enjoyable experience. Of course, I always like to tell stories, so it's fun for me.

Hughes: Well, I enjoyed hearing them, and I thank you.

Transcribed by Jessica Ross Stern
Final Typed by Kathy Zvanovec-Higbee

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1978 - 1986 Molecular Biologist, Senior Research Scientist,
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Expression in *E. coli* of chemically synthesized genes for human insulin." Proc. Natl. Acad. Sci. USA 76, 106 (1979).

Benchmark Papers in Organic Chemistry
1975 "Oligonucleotide synthesis on polar polymer supports. The use of a polypeptide support." J.C.S. Chem. Commun. 193 (1973).

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Registered Patent Agent, United States Department of Commerce Patent and Trademark Office 1986, Registration No. 32,037.

GRANT AWARDS

Grant No. 1 R01 CA 21593-1
1977 "Mechanism of carcinogen induced frame shift mutations."

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Grant No. 1 F32 HD 05097-1
1975 National Institutes of Health, Public Health Service Fellow

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1972 National Institutes of Health, Postdoctoral Fellow

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USP 4,663,283 Method of Altering Double-Stranded DNA. (Genentech, Inc.)

D.G. Kleid, W. Kohr and F. Thiebodeau
USP 5,152,969 and 5,162,105 Method of Extracting Gold From its Ores. (Geobiotics, Inc.)

D.G. Kleid, D.G. Yansura, H.L. Heyneker and G. Miozarri
USP 5,888,808 & 6,333,174 Bacterial Polypeptide Expression Employing Tryptophan Promoter-Operator. (Genentech, Inc.)

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European Patent Application 068693. Production of Foot-and-Mouth Disease Vaccine from microbially expressed antigens thereof. (Genentech, Inc.)

PUBLISHED FEDERAL DISTRICT COURT, CAFC, AND PTO DECISIONS*

*[Of course my name is not on any of these cases, but since 1985 I have been working in the area of patent litigation. These are some of the published decisions on the Genentech's cases on which I worked.]

Scripps Clinic & Research Fd., Revlon, & Rorer *vs* Genentech Inc., Miles, & Chiron
(C-83-5423-WWS, & C-83-5424-WWS N.D. Ca)
231 USPQ 978 (N.D. Cal. 1986)
3 USPQ2d 1481 (N.D. Cal. 1987)
6 USPQ2d 1018 (N.D. Cal. 1988)
11 USPQ2d 1187 (N.D. Cal. 1989)
12 USPQ2d 1157 (N.D. Cal. 1989)
18 USPQ2d 1001 (Fed. Cir. 1991)
18 USPQ2d 1896 (Fed. Cir. 1991)

Hormone Research Fd., Inc. & Hoffmann-LaRoche, Inc. *vs* Genentech
(C-86-5201 MHP N.D. Ca.)
8 USPQ2d 1377 (N.D. Cal. 1988)
15 USPQ2d 1039 (Fed. Cir. 1990) cert. dismissed, 111 S. Ct. 1434, 499 U.S. 995 (1991)

Genentech *vs* Abbott Lab.
(C 88-0889 MHP N.D. CA)
10 USPQ2d 1871 (N.D. Cal. 1989)

Genentech et al. *vs* Wellcome, Genetics Institute, et al.
(CA 88-407, 89-330 D. Del)
14 USPQ2d 1363 (D. Del. 1990)
24 USPQ2d 1782 (D. Del. 1992)
28 USPQ2d 1633 (D. Del. 1993)
31 USPQ2d 1161 (Fed. Cir. 1994)

In re Recombinant DNA Technology Patent and Contract Litig.,
[MDL Docket No. MDL 912: Lilly *vs* GNE IP-87-0219-C (S.D. Ind.), GNE *vs* Lilly IP-88-1463-C (S.D. Ind.), UC *vs* Lilly 90-0373-DLJ (N.D. Ca), GNE *vs* Lilly & UC IP-90-1679-C-D/G (S.D. Ind.), UC *vs* GNE IP 90-2232 RFP/CAL (N.D. CA) UC *vs* GNE IP-92-0223-C (S.D. Ind.), UC *vs* GNE 97-2563 SI/CAL N.D. Ca]
5 USPQ2d 1902 (S.D. Ind. 1987)
14 USPQ2d 1909 (N.D. Cal. 1990)
17 USPQ2d 1531 (S.D. Ind. 1991)
19 USPQ2d 1668 (N.D. Cal. 1991)
21 USPQ2d 1201 (N.D. Cal. 1992)
22 USPQ2d 1748, 964 (Fed. Cir. 1992)
27 USPQ2d 1241 (Fed. Cir. 1993) cert. denied, 114 S. Cr. 1126, 127 L. Ed. 2d 434 (1994)
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34 USPQ2d 1097 (S.D. Ind. 1994)
39 USPQ2d 1225 (S.D. Ind. 1995)
40 USPQ2d 1768 (S.D. Ind. 1996)
40 USPQ2d 1784 (Fed. Cir. 1996)
43 USPQ2d 1398 (Fed. Cir. 1997)
46 USPQ2d 1586 (Fed. Cir. 1998)

In the Matter of Certain Recombinantly Produced Human Growth Hormones
Genentech *vs* Novo Nordisk & Bio-Technology Gen. Corp.
ITC Inv. No. 337-TA-358 (ITC 1/17/95, Pub. version 2/13/95)
43 USPQ2d 1722 (Fed. Cir. 1997)

Bio-Technology Gen. Corp. *vs* Genentech
(95-Civ-0110 CBM; 95-Civ-0110-TPG S.D. N.Y)
36 USPQ2d 1169 (S.D. N.Y. 1995)
38 USPQ2d 1321 (Fed. Cir. 1996)
60 USPQ2d 1430 (Fed. Cir. 2001)

Novo Nordisk of North Am., Inc. *vs* Genentech Inc.
(94-8634 CBM S.D. N.Y.)
35 USPQ2d 1058 (S.D. N.Y. 1995)
36 USPQ2d 1286 (S.D. N.Y. 1995)
37 USPQ2d 1773 (Fed. Cir. 1996)
935 F. Supp 260 (S.D. N.Y. 1996)
42 USPQ2d 1001 (Fed. Cir. 1997)

Genentech, Inc. *vs* Chiron Corp.
(CV 94-3334 CW, N.D. Cal.) (§146 Appeal from Patent Interference Lee *vs* Barr No. 102,208)
1995 WL 450846 (N.D. Cal. 1995)
42 USPQ2d 1608 (Fed. Cir. 1997)
55 USPQ2d 1636 (Fed. Cir. 2000)

Singh *vs* Brake (Genentech *vs* Chiron)
(CAFC No. 99-1259) (§141 Appeal from Patent Interference Singh v Brake.)
55 USPQ2d 1673 (Fed. Cir. 2000)

Hitzeman *vs* Rutter (Genentech *vs* U. of Cal.)
(CAFC No. 99-1604, No. 99-1605) (§141 Appeal from Patent Interferences Hitzeman *vs* Rutter Nos. 102,416 & 102,989)
58 USPQ2d 1161 (Fed. Cir. 2001)

Ex Parte Goeddel
5 USPQ2d 1449 (BPAI 1987)

Ex Parte Hitzeman (86-1753)
9 USPQ2d 1821 (BPAI 1988)

Ex Parte Gray (88-0437)
10 USPQ2d 1922 (BPAI 1989)

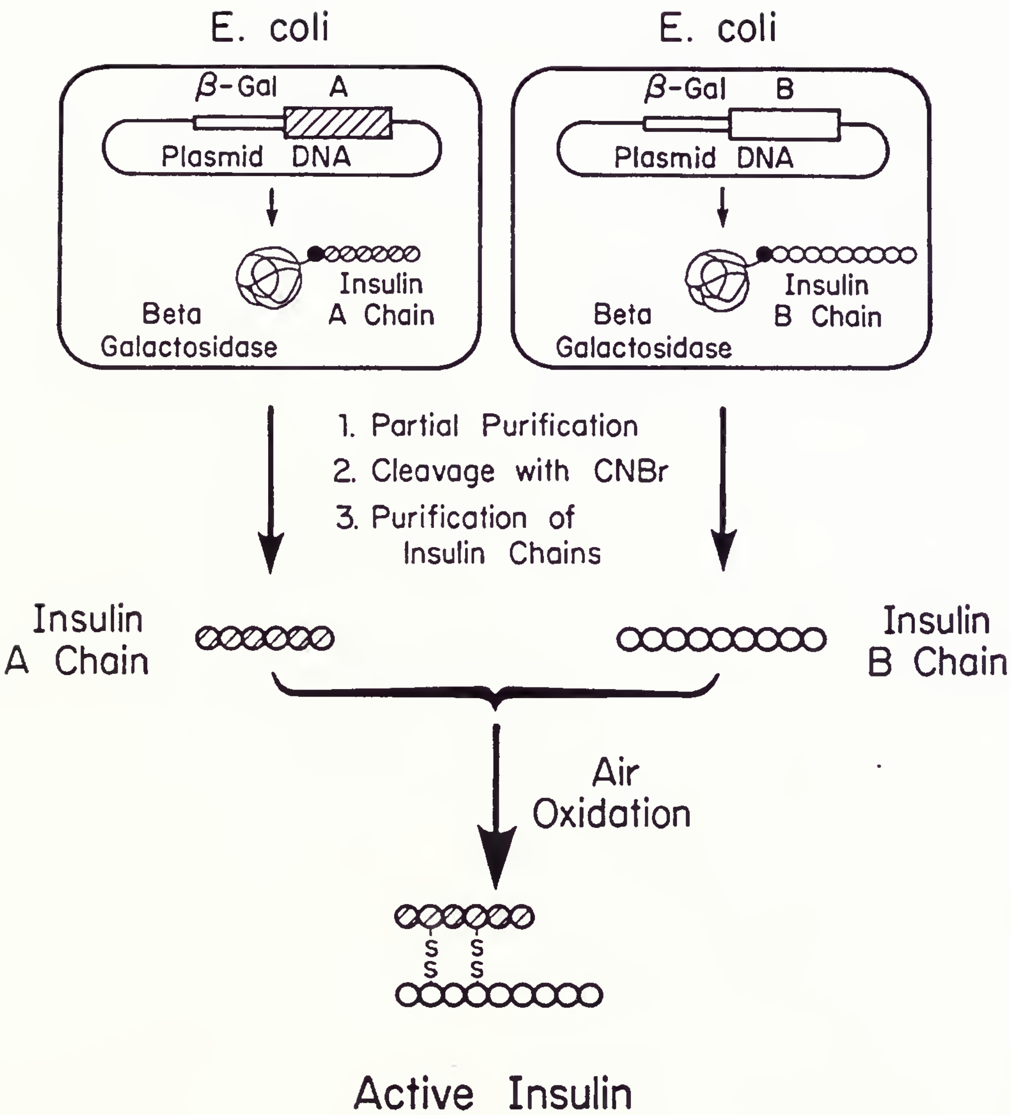
Ex Parte Aggarwal (90-3041)
23 USPQ2d 1334 (BPAI 1992)

Cabilly *vs* Boss PTO interference no. 102,572
55 USPQ2d 1238 (BPAI 1998)
60 USPQ2d 1752 (BPAI 2001)

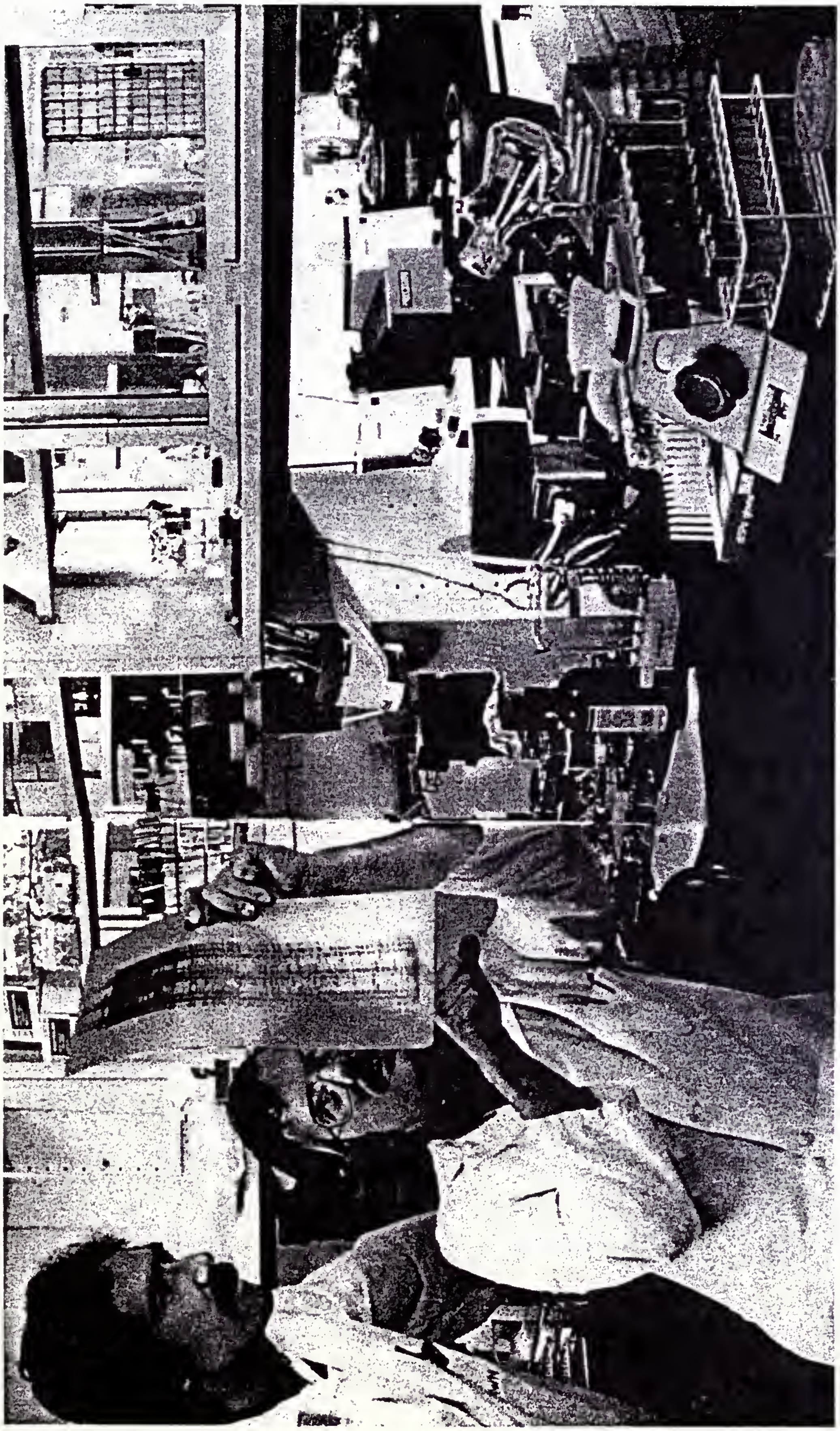
Yamada *vs* Aggarwal PTO interference no. 103,605
57 USPQ2d 2002 (BPAI 2000)

Genentech Awards

Date:	Supervisor:
31-JUL-2002	SEAN JOHNSTON
31-OCT-2000	SEAN JOHNSTON
29-JUN-1995	STEPHEN R. RAINES
03-JAN-1995	STEPHEN R. RAINES
26-JUL-1993	STEPHEN R. RAINES
20-JAN-1993	STEPHEN R. RAINES
05-JUN-1992	STEPHEN R. RAINES
05-NOV-1991	STEPHEN R. RAINES
10-APR-1990	STEPHEN R. RAINES
24-JUL-1989	JOHN MC LAUGHLIN
06-NOV-1987	BRIAN CUNNINGHAM



Genentech's Method for Producing Recombinant Human Insulin



Photograph of Richard Lawn (left) and Dennis Kleid (right) in a Genentech Molecular Biology Laboratory, 1979

Photomicrograph of *E. coli* showing refractile bodies, taken at Plum Island Animal Disease Center in Greenport, New York using a phase contrast microscope, circa 1980

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

Distribution:

P. Berman
C. Czarniecki
D. Kleid
L. Lasky
E. Patzer
S. Shire

Internal Correspondence

Date: February 11, 1983

To: Distribution

From: Jack Obijeski

Subject: GOAL SETTING, 1983

To follow-up on my memo of January 3, 1983, I would like to meet with each of you next week to discuss your goals for 1983. Please formalize your individual goals and priorities and tie these to Genentech's Corporate Goals (attached). Please coordinate with Katie a time so we can meet. I apologize for the delay in the goal-setting process, but the corporate goals have only recently been agreed upon.

G. [illegible]

1983 CORPORATE GOALS

1. To manage the Company's growth, revenue, and expenses for 1983 to "break even" for the year. To pursue sufficient additional revenues to allow a cushion for slippage, or a profit if everything happens.

2. To achieve the following goals on our "top five" product development projects:

A.	Human Growth Hormone	- FDA approval for marketing, 3rd Quarter
		- Begin clinical trials for Turner's Syndrome, 1st Quarter; For CSS, 2nd Quarter; Cachexia, 3rd Quarter
		- Develop an alternative dosage form, 4th Quarter.
B.	Tissue Plasminogen Activator	- File IND 2nd Quarter
		- Produce sufficient material for Japanese and European clinicals (2 grams), 3rd Quarter
		- Begin Phase II Clinical Trials for MI, 4th Quarter
		- Develop bacterial or yeast alternative production system and compare material.
C.	Gamma Interferon	- File IND, 1st Quarter
		- Begin Phase II Clinicals for anti-cancer, 3rd Quarter
		- Begin Phase II Clinicals for anti-viral, 4th Quarter.
D.	Bovine Interferon	- Complete dose titration studies, 1st Quarter
		- Begin Field Trials, 3rd Quarter
		- Bring yield into economic range, 4th Quarter.
		- Evaluate antiviral efficacy of Alpha 4 and Beta 2 by 3rd Quarter.

E. Hepatitis Vaccine

- Obtain FDA approval for cell line, 1st Quarter
- File IND, 2nd Quarter
- Begin Phase I Clinicals, 3rd Quarter
- Establish commercial marketing agreement, 3rd Quarter.

3. To successfully launch our first product, human growth hormone. To build the marketing and sales forces needed for introduction and the accounting, control and information systems needed for marking this product.

4. To bring our manufacturing facility to full operation, and to pass FDA's validation inspection by 2nd Quarter.

5. To build technical expertise and capabilities in the following area

   - Formulation and alternative delivery systems
   - Protein engineering
   - Pharmacology
   - Large-scale tissue culture
   - Clinical.

6. To sign at least 14 major marketing agreements for revenue generation as a part of a program for early product entry in Europe and Japan, and to capture full value for our reesearch investment:

   Pharmaceutical - 5

   Agricultural - 5

   Industrial - 2.

7. To develop commercially viable secretion systems in bacillus, yeast and pseudomonas, and to establish this approach as the best way of manufacturing one of our important products.

8. Control spending and financial reporting by:
   - Identifying and implementing new MIS business systems
   - Establishing charge outs for critical variable expenses
   - Developing a formal review process for budget-to-actual cost center performance.

9. To fulfill key business commitments beyond the top five projects.

Pharmaceutical

- Develop HSA secretion system by 12/83
- Express two lymphokines (lymphotoxin, Interleukin II, Tumor Necrosis Factor) by 12/83
- C-terminal amidation of calcitonin by 6/83
- Produce 4 grams of FIF bv 4/83
- Express Factor VIII by 12/83
- Express at least two oncogenes by 12/83
- Express relaxin, EGF and a possibly useful therapeutic anti-body.

Industrial

- Rennin
  - o Develop 1000 liter process with a cost target no greater than $[redacted]/gram by 12/83
  - o Manufacture 300 grams of material for large scale cheese trials by 10/83
- Clone and express: prenyl transferase by 3rd Quarter (Project Unicorn); 2.5 - DKG reductase by 4th Quarter (Ascorbic Acid); and an engineered family of alkaline pro-teases by 4th Quarter.

Agricultural

- Express porcine interferon by 6/83 and produce sufficient quantity for initial in vivo and in vitro testing by 9/83
- Express chicken interferon by 9/83 and produce sufficient quantity for in vitro testing by 12/83
- Develop process for chicken growth hormone and produce 100 mg at 95% pure by 3/30/83
- Start developing alternative dosage and delivery systems for agricultural products beginning with chicken growth hormone in 1st Quarter.
- Prove efficacy in cattle of one FMD subtype; carry out successful Columbia Field Trials with partner by end of 1983.

10. To continue to conduct outstanding research, while establishing a long-term research and development strategy to build on our current strengths.

11. To attract and motivate outstanding people and continue to build an excited, results-oriented team that "makes things happen". To assur that we recruit only quality individuals with special emphasis on a significant number of key senior positions. To establish a corporat framework for future growth and expand our organizational developmer and management training programs.

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